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(54) Title: NOVEL G PROTEIN-COUPLED RECEPTORS

(57) Abstract: The present invention provides a gene encoding a G protein-coupled receptor termed nGPCR-x; constructs and recombinant host cells incorporating the genes; the nGPCR-x polypeptides encoded by the gene; antibodies to the nGPCR-x polypeptides; and methods of making and using all of the foregoing.

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## NOVEL G PROTEIN-COUPLED RECEPTORS

### CROSS-REFERENCE TO RELATED APPLICATIONS

- [0001] The present application claims priority of Application Serial No. 60/189,783, filed 2000 March 16; Application Serial No. 60/189,918 filed 2000 March 16; Application Serial No. 60/189,960 filed 2000 March 16; Application Serial No. 60/189,917 filed 2000 March 16; Application Serial No. 60/189,907 filed 2000 March 16; Application Serial No. 60/192,945 filed 2000 March 29; Application Serial No. 60/192,916 filed 2000 March 29; Application Serial No. 60/192,923 filed 2000 March 29; Application Serial No. 60/192,933 filed 2000 March 29; Application Serial No. 60/192,830 filed 2000 March 29; Application Serial No. 60/192,234 filed 2000 March 29; Application Serial No. 60/192,155 filed 2000 March 29; Application Serial No. 60/192,935 filed 2000 March 29; each of which is hereby incorporated by reference in its entirety.

### FIELD OF THE INVENTION

- [0002] The present invention relates generally to the fields of genetics and cellular and molecular biology. More particularly, the invention relates to novel G protein coupled receptors, to polynucleotides that encode such novel receptors, to reagents such as antibodies, probes, primers and kits comprising such antibodies, probes, primers related to the same, and to methods which use the novel G protein coupled receptors, polynucleotides or reagents.

### BACKGROUND OF THE INVENTION

- [0003] The G protein-coupled receptors (GPCRs) form a vast superfamily of cell surface receptors which are characterized by an amino-terminal extracellular domain, a carboxyl-terminal intracellular domain, and a serpentine structure that passes through the cell membrane seven times. Hence, such receptors are sometimes also referred to as seven transmembrane (7TM) receptors. These seven transmembrane domains define three extracellular loops and three intracellular loops, in addition to the amino- and carboxy-terminal domains. The extracellular portions of the receptor have a role in recognizing and binding one or more extracellular binding partners (*e.g.*, ligands), whereas the intracellular portions have a role in recognizing and communicating with downstream molecules in the signal transduction cascade.

[0004] The G protein-coupled receptors bind a variety of ligands including calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and even photons, and are important in the normal (and sometimes the aberrant) function of many cell types. [See generally Strosberg, *Eur. J. Biochem.* 196:1-10 (1991) and Bohmet *al.*, *Biochem J.* 322:1-18 (1997).] When a specific ligand binds to its corresponding receptor, the ligand typically stimulates the receptor to activate a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) that is coupled to the intracellular portion of the receptor. The G protein in turn transmits a signal to an effector molecule within the cell, by either stimulating or inhibiting the activity of that effector molecule. These effector molecules include adenylate cyclase, phospholipases and ion channels. Adenylate cyclase and phospholipases are enzymes that are involved in the production of the second messenger molecules cAMP, inositol triphosphate and diacylglycerol. It is through this sequence of events that an extracellular ligand stimuli exerts intracellular changes through a G protein-coupled receptor. Each such receptor has its own characteristic primary structure, expression pattern, ligand-binding profile, and intracellular effector system.

[0005] Because of the vital role of G protein-coupled receptors in the communication between cells and their environment, such receptors are attractive targets for therapeutic intervention, for example by activating or antagonizing such receptors. For receptors having a known ligand, the identification of agonists or antagonists may be sought specifically to enhance or inhibit the action of the ligand. Some G protein-coupled receptors have roles in disease pathogenesis (*e.g.*, certain chemokine receptors that act as HIV co-receptors may have a role in AIDS pathogenesis), and are attractive targets for therapeutic intervention even in the absence of knowledge of the natural ligand of the receptor. Other receptors are attractive targets for therapeutic intervention by virtue of their expression pattern in tissues or cell types that are themselves attractive targets for therapeutic intervention. Examples of this latter category of receptors include receptors expressed in immune cells, which can be targeted to either inhibit autoimmune responses or to enhance immune responses to fight pathogens or cancer; and receptors expressed in the brain or other neural organs and tissues, which are likely targets in the treatment of mental disorder, depression, bipolar disease, or other neurological disorders. This latter category of receptor is also useful as a marker for identifying and/or purifying (*e.g.*, via fluorescence-activated cell sorting) cellular subtypes that express the receptor. Unfortunately, only a limited number of G protein receptors from the central nervous system (CNS) are known. Thus, a need exists for G protein-coupled receptors that have been identified and show promise as targets for therapeutic intervention in a variety of animals, including humans.

## SUMMARY OF THE INVENTION

- [0006] The present invention relates to an isolated nucleic acid molecule that comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, or a fragment thereof. The nucleic acid molecule encodes at least a portion of nGPCR $\alpha$ . In some embodiments, the nucleic acid molecule comprises a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or a fragment thereof. In some embodiments, the nucleic acid molecule comprises a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, and fragments thereof.
- [0007] According to some embodiments, the present invention provides vectors which comprise the nucleic acid molecule of the invention. In some embodiments, the vector is an expression vector.
- [0008] According to some embodiments, the present invention provides host cells which comprise the vectors of the invention. In some embodiments, the host cells comprise expression vectors.
- [0009] The present invention provides an isolated nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, said portion comprising at least 10 nucleotides.
- [00010] The present invention provides a method of producing a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, or a homolog or fragment thereof. The method comprising the steps of introducing a recombinant expression vector that includes a nucleotide sequence that encodes the polypeptide into a compatible host cell, growing the host cell under conditions for expression of the polypeptide and recovering the polypeptide.
- [00011] The present invention provides an isolated antibody which binds to an epitope on a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, or a homolog or fragment thereof.
- [00012] The present invention provides a method of inducing an immune response in a mammal against a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, or a homolog or fragment thereof. The method comprises



administering to a mammal an amount of the polypeptide sufficient to induce said immune response.

[00013] The present invention provides a method for identifying a compound which binds nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether the compound binds nGPCR-x.

[00014] The present invention provides a method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x. The method comprises the steps of contacting said nucleic acid molecule encoding nGPCR-x with a compound and determining whether said compound binds said nucleic acid molecule.

[00015] The present invention provides a method for identifying a compound which modulates the activity of nGPCR-x. The method comprises the steps of contacting nGPCR-x with a compound and determining whether nGPCR-x activity has been modulated.

[00016] The present invention provides a method of identifying an animal homolog of nGPCR-x. The method comprises the steps screening a nucleic acid database of the animal with a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or a portion thereof and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or portion thereof.

[00017] The present invention provides a method of identifying an animal homolog of nGPCR-x. The methods comprises the steps screening a nucleic acid library of the animal with a nucleic acid molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or a portion thereof, and determining whether a portion of said library or database is homologous to said sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or a portion thereof.

[00018] Another aspect of the present invention relates to methods of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor. The methods comprise the steps of assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR-x that is expressed in the brain. The nGPCR-x comprise an amino acid sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, and allelic variants thereof. A diagnosis of the disorder or predisposition is made from the presence or absence of the mutation. The presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR-x in the nucleic acid correlates with an increased risk of developing the disorder.

[00019] The present invention further relates to methods of screening for a nGPCR-x hereditary mental disorder genotype in a human patient. The methods comprise the steps of providing a

biological sample comprising nucleic acid from the patient, in which the nucleic acid includes sequences corresponding to alleles of nGPCR-x. The presence of one or more mutations in the nGPCR-x allele is indicative of a hereditary mental disorder genotype.

[00020] The present invention provides kits for screening a human subject to diagnose mental disorder or a genetic predisposition therefor. The kits include an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x gene. The oligonucleotide comprises 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution. The kit also includes a media packaged with the oligonucleotide. The media contains information for identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

[00021] The present invention further relates to methods of identifying nGPCR-x allelic variants that correlates with mental disorders. The methods comprise the steps of providing biological samples that comprise nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny, and detecting in the nucleic acid the presence of one or more mutations in an nGPCR-x that is expressed in the brain. The nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, and allelic variants thereof. The nucleic acid includes sequences corresponding to the gene or genes encoding nGPCR-x. The one or more mutations detected indicate an allelic variant that correlates with a mental disorder.

[00022] The present invention further relates to purified polynucleotides comprising nucleotide sequences encoding alleles of nGPCR-x from a human with mental disorder. The polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 under the following hybridization conditions: (a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS. The polynucleotide that encodes nGPCR-x amino acid sequence of the human differs from a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257 by at least one residue.

[00023] The present invention also provides methods for identifying a modulator of biological activity of nGPCR-x comprising the steps of contacting a cell that expresses nGPCR-x in the presence and in the absence of a putative modulator compound and measuring nGPCR-x biological activity in the cell. The decreased or increased nGPCR-x biological activity in the

presence versus absence of the putative modulator is indicative of a modulator of biological activity.

[00024] The present invention further provides methods to identify compounds useful for the treatment of mental disorders. The methods comprise the steps of contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x. The binding between nGPCR-x and the compound suspected of binding nGPCR-x is detected. Compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of mental disorder. Compounds identified as binding nGPCR-x may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

[00025] The present invention further provides methods for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x. The methods comprise the steps of contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound and detecting binding between the binding partner and nGPCR-x. Decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a related disease or disorder. Compounds identified as modulating binding between nGPCR-x and a nGPCR-x binding partner may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

[00026] Another aspect of the present invention relates to methods of purifying a G protein from a sample containing a G protein. The methods comprise the steps of contacting the sample with an nGPCR-x for a time sufficient to allow the G protein to form a complex with the nGPCR-x; isolating the complex from remaining components of the sample; maintaining the complex under conditions which result in dissociation of the G protein from the nGPCR-x; and isolating said G protein from the nGPCR-x.

## DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

### Definitions

[00027] Various definitions are made throughout this document. Most words have the meaning that would be attributed to those words by one skilled in the art. Words specifically defined either below or elsewhere in this document have the meaning provided in the context of the present invention as a whole and as are typically understood by those skilled in the art.

[00028] "Synthesized" as used herein and understood in the art, refers to polynucleotides produced by purely chemical, as opposed to enzymatic, methods. "Wholly" synthesized DNA

sequences are therefore produced entirely by chemical means, and "partially" synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means.

[00029] By the term "region" is meant a physically contiguous portion of the primary structure of a biomolecule. In the case of proteins, a region is defined by a contiguous portion of the amino acid sequence of that protein.

[00030] The term "domain" is herein defined as referring to a structural part of a biomolecule that contributes to a known or suspected function of the biomolecule. Domains may be co-extensive with regions or portions thereof; domains may also incorporate a portion of a biomolecule that is distinct from a particular region, in addition to all or part of that region. Examples of GPCR protein domains include, but are not limited to, the extracellular (*i.e.*, N-terminal), transmembrane and cytoplasmic (*i.e.*, C-terminal) domains, which are co-extensive with like-named regions of GPCRs; each of the seven transmembrane segments of a GPCR; and each of the loop segments (both extracellular and intracellular loops) connecting adjacent transmembrane segments.

[00031] As used herein, the term "activity" refers to a variety of measurable indicia suggesting or revealing binding, either direct or indirect; affecting a response, *i.e.* having a measurable affect in response to some exposure or stimulus, including, for example, the affinity of a compound for directly binding a polypeptide or polynucleotide of the invention, or, for example, measurement of amounts of upstream or downstream proteins or other similar functions after some stimulus or event.

[00032] Unless indicated otherwise, as used herein, the abbreviation in lower case (*gpcr*) refers to a gene, cDNA, RNA or nucleic acid sequence, while the upper case version (*GPCR*) refers to a protein, polypeptide, peptide, oligopeptide, or amino acid sequence. The term "nGPCR-x" refers to any of the nGPCRs taught herein, while specific reference to a nGPCR (for example nGPCR-2073) refers only to that specific nGPCR.

[00033] As used herein, the term "antibody" is meant to refer to complete, intact antibodies, and Fab, Fab', F(ab)2, and other fragments thereof. Complete, intact antibodies include monoclonal antibodies such as murine monoclonal antibodies, chimeric antibodies and humanized antibodies.

[00034] As used herein, the term "binding" means the physical or chemical interaction between two proteins or compounds or associated proteins or compounds or combinations thereof. Binding includes ionic, non-ionic, Hydrogen bonds, Van der Waals, hydrophobic interactions, etc. The physical interaction, the binding, can be either direct or indirect, indirect being through or due to the effects of another protein or compound. Direct binding refers to interactions that do not take place through or due to the effect of another protein or compound but instead are

without other substantial chemical intermediates. Binding may be detected in many different manners. As a non-limiting example, the physical binding interaction between a nGPCR-x of the invention and a compound can be detected using a labeled compound. Alternatively, functional evidence of binding can be detected using, for example, a cell transfected with and expressing a nGPCR-x of the invention. Binding of the transfected cell to a ligand of the nGPCR-x that was transfected into the cell provides functional evidence of binding. Other methods of detecting binding are well known to those of skill in the art.

- [00035] As used herein, the term "compound" means any identifiable chemical or molecule, including, but not limited to, small molecule, peptide, protein, sugar, nucleotide, or nucleic acid, and such compound can be natural or synthetic.
- [00036] As used herein, the term "complementary" refers to Watson-Crick basepairing between nucleotide units of a nucleic acid molecule.
- [00037] As used herein, the term "contacting" means bringing together, either directly or indirectly, a compound into physical proximity to a polypeptide or polynucleotide of the invention. The polypeptide or polynucleotide can be in any number of buffers, salts, solutions *etc.* Contacting includes, for example, placing the compound into a beaker, microtiter plate, cell culture flask, or a microarray, such as a gene chip, or the like, which contains the nucleic acid molecule, or polypeptide encoding the nGPCR or fragment thereof.
- [00038] As used herein, the phrase "homologous nucleotide sequence," or "homologous amino acid sequence," or variations thereof, refers to sequences characterized by a homology, at the nucleotide level or amino acid level, of at least the specified percentage. Homologous nucleotide sequences include those sequences coding for isoforms of proteins. Such isoforms can be expressed in different tissues of the same organism as a result of, for example, alternative splicing of RNA. Alternatively, isoforms can be encoded by different genes. Homologous nucleotide sequences include nucleotide sequences encoding for a protein of a species other than humans, including, but not limited to, mammals. Homologous nucleotide sequences also include, but are not limited to, naturally occurring allelic variations and mutations of the nucleotide sequences set forth herein. A homologous nucleotide sequence does not, however, include the nucleotide sequence encoding other known GPCRs. Homologous amino acid sequences include those amino acid sequences which contain conservative amino acid substitutions and which polypeptides have the same binding and/or activity. A homologous amino acid sequence does not, however, include the amino acid sequence encoding other known GPCRs. Percent homology can be determined by, for example, the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, Madison WI), using the default settings, which uses the algorithm of Smith and

Waterman (Adv. Appl. Math., 1981, 2, 482-489, which is incorporated herein by reference in its entirety).

- [00039] As used herein, the term "isolated" nucleic acid molecule refers to a nucleic acid molecule (DNA or RNA) that has been removed from its native environment. Examples of isolated nucleic acid molecules include, but are not limited to, recombinant DNA molecules contained in a vector, recombinant DNA molecules maintained in a heterologous host cell, partially or substantially purified nucleic acid molecules, and synthetic DNA or RNA molecules.
- [00040] As used herein, the terms "modulates" or "modifies" means an increase or decrease in the amount, quality, or effect of a particular activity or protein.
- [00041] As used herein, the term "oligonucleotide" refers to a series of linked nucleotide residues which has a sufficient number of bases to be used in a polymerase chain reaction (PCR). This short sequence is based on (or designed from) a genomic or cDNA sequence and is used to amplify, confirm, or reveal the presence of an identical, similar or complementary DNA or RNA in a particular cell or tissue. Oligonucleotides comprise portions of a DNA sequence having at least about 10 nucleotides and as many as about 50 nucleotides, preferably about 15 to 30 nucleotides. They are chemically synthesized and may be used as probes.
- [00042] As used herein, the term "probe" refers to nucleic acid sequences of variable length, preferably between at least about 10 and as many as about 6,000 nucleotides, depending on use. They are used in the detection of identical, similar, or complementary nucleic acid sequences. Longer length probes are usually obtained from a natural or recombinant source, are highly specific and much slower to hybridize than oligomers. They may be single or double-stranded and carefully designed to have specificity in PCR, hybridization membrane-based, or ELISA-like technologies.
- [00043] The term "preventing" refers to decreasing the probability that an organism contracts or develops an abnormal condition.
- [00044] The term "treating" refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.
- [00045] The term "therapeutic effect" refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of the following: (a) an increase in the proliferation, growth, and/or differentiation of cells; (b) inhibition (*i.e.*, slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition; and (e) enhancing the function of the

affected population of cells. Compounds demonstrating efficacy against abnormal conditions can be identified as described herein.

[00046] The term "abnormal condition" refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, cell signaling, or cell survival. An abnormal condition may also include obesity, diabetic complications such as retinal degeneration, and irregularities in glucose uptake and metabolism, and fatty acid uptake and metabolism.

[00047] Abnormal cell proliferative conditions include cancers such as fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation.

[00048] Abnormal differentiation conditions include, but are not limited to, neurodegenerative disorders, slow wound healing rates, and slow tissue grafting/healing rates. Abnormal cell signaling conditions include, but are not limited to, psychiatric disorders involving excess neurotransmitter activity.

[00049] Abnormal cell survival conditions may also relate to conditions in which programmed cell death (apoptosis) pathways are activated or abrogated. A number of protein kinases are associated with the apoptosis pathways. Aberrations in the function of any one of the protein kinases could lead to cell immortality or premature cell death.

[00050] The term "administering" relates to a method of incorporating a compound into cells or tissues of an organism. The abnormal condition can be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques and carrier techniques.

[00051] The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism. The effect of administering a compound on organism function can then be monitored. The organism is preferably a mouse, rat, rabbit, guinea pig or goat, more preferably a monkey or ape, and most preferably a human.

[00052] By "amplification" it is meant increased numbers of DNA or RNA in a cell compared with normal cells. "Amplification" as it refers to RNA can be the detectable presence of RNA in cells, since in some normal cells there is no basal expression of RNA. In other normal cells, a

basal level of expression exists, therefore in these cases amplification is the detection of at least 1 to 2-fold, and preferably more, compared to the basal level.

[00053] As used herein, the phrase "stringent hybridization conditions" or "stringent conditions" refers to conditions under which a probe, primer, or oligonucleotide will hybridize to its target sequence, but to no other sequences. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. Generally, stringent conditions are selected to be about 5°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target sequence hybridize to the target sequence at equilibrium. Since the target sequences are generally present in excess, at  $T_m$ , 50% of the probes are occupied at equilibrium. Typically, stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes, primers or oligonucleotides (e.g. 10 to 50 nucleotides) and at least about 60°C for longer probes, primers or oligonucleotides. Stringent conditions may also be achieved with the addition of destabilizing agents, such as formamide.

[00054] The amino acid sequences are presented in the amino to carboxy direction, from left to right. The amino and carboxy groups are not presented in the sequence. The nucleotide sequences are presented by single strand only, in the 5' to 3' direction, from left to right. Nucleotides and amino acids are represented in the manner recommended by the IUPAC-IUB Biochemical Nomenclature Commission or (for amino acids) by three letters code.

#### **Polynucleotides**

[00055] The present invention provides purified and isolated polynucleotides (e.g., DNA sequences and RNA transcripts, both sense and complementary antisense strands, both single and double-stranded, including splice variants thereof) that encode unknown G protein-coupled receptors heretofore termed novel GPCRs, or nGPCRs. These genes are described herein and designated herein collectively as nGPCR-x (where x is 2227-2229, 2280-2286, 2469-2479, 2480-2489, 2490-2499, 2500-2506, 2507-2516, 2517-2526, 2527-2536, 2537-2548, 2550-2554, 2555-2565, 2566-2576, and 2577-2587). Table 1 below identifies the novel gene sequence nGPCR-x designation, the SEQ ID NO: of the gene sequence, the SEQ ID NO: of the polypeptide encoded thereby, and the U.S. Provisional Application in which the gene sequence has been disclosed.

**Table 1**

nGPCR	Nucleotide Sequence	Amino acid Sequence	Originally filed in:	nGPCR	Nucleotide Sequence	Amino acid Sequence	Originally filed in:
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	(SEQ ID NO:)	(SEQ ID NO:)			(SEQ ID NO:)	(SEQ ID NO:)	
2227	1	129	A		2523	65	193
2228	2	130	A		2524	66	194
2229	3	131	A		2525	67	195
2280	4	132	A		2526	68	196
2281	5	133	A		2527	69	197
2282	6	134	A		2528	70	198
2283	7	135	A		2529	71	199
2284	8	136	A		2530	72	200
2285	9	137	A		2531	73	201
2286	10	138	A		2532	74	202
2469	11	139	B		2533	75	203
2470	12	140	B		2534	76	204
2471	13	141	B		2535	77	205
2472	14	142	B		2536	78	206
2473	15	143	B		2537	79	207
2474	16	144	B		2538	80	208
2475	17	145	B		2539	81	209
2476	18	146	B		2540	82	210
2477	19	147	B		2541	83	211
2478	20	148	B		2542	84	212
2479	21	149	B		2543	85	213
2480	22	150	C		2544	86	214
2481	23	151	C		2545	87	215
2482	24	152	C		2546	88	216
2483	25	153	C		2547	89	217
2484	26	154	C		2548	90	218
2485	27	155	C		2550	91	219
2486	28	156	C		2551	92	220
2487	29	157	C		2552	93	221
2488	30	158	C		2553	94	222
2489	31	159	C		2554	95	223
2490	32	160	D		2555	96	224
2491	33	161	D		2556	97	225
2492	34	162	D		2557	98	226
2493	35	163	D		2558	99	227
2494	36	164	D		2559	100	228
2495	37	165	D		2560	101	229
2496	38	166	D		2561	102	230
2497	39	167	D		2562	103	231
2498	40	168	D		2563	104	232
2499	41	169	D		2564	105	233
2500	42	170	E		2565	106	234
2501	43	171	E		2566	107	235
2502	44	172	E		2567	108	236
2503	45	173	E		2568	109	237
2504	46	174	E		2569	110	238
2505	47	175	E		2570	111	239
2506	48	176	E		2571	112	240
2507	49	177	F		2572	113	241
2508	50	178	F		2573	114	242
2509	51	179	F		2574	115	243
2510	52	180	F		2575	116	244
2511	53	181	F		2576	117	245
2512	54	182	F		2577	118	246
2513	55	183	F		2578	119	247
2514	56	184	F		2579	120	248
2515	57	185	F		2580	121	249
2516	58	186	F		2581	122	250, 251
2517	59	187	G		2582	123	252
2518	60	188	G		2583	124	253
2519	61	189	G		2584	125	254
2520	62	190	G		2585	126	255
2521	63	191	G		2586	127	256
2522	64	192	G		2587	128	257

### Legend

A= Ser. No. 60/189,783  
 C= Ser. No. 60/189,960  
 E= Ser. No. 60/189,907  
 G= Ser. No. 60/192,916  
 I= Ser. No. 60/192,933  
 K= Ser. No. 60/192,234  
 M= Ser. No. 60/192,935

B= Ser. No. 60/189,918  
 D= Ser. No. 60/189,917  
 F= Ser. No. 60/192,945  
 H= Ser. No. 60/192,923  
 J= Ser. No. 60/192,830  
 L= Ser. No. 60/192,155

[00056] When a specific nGPCR is identified (for example nGPCR-2285), it is understood that only that specific nGPCR is being referred to.

[00057] It is well known that GPCRs are expressed in many different tissues, including the brain. Accordingly, the nGPCR-x of the present invention may be useful, *inter alia*, for treating and/or diagnosing mental disorders. Following the techniques described in Example 5, below, those skilled in the art could readily ascertain if nGPCR-x is expressed in a particular tissue or region.

[00058] The invention provides purified and isolated polynucleotides (*e.g.*, cDNA, genomic DNA, synthetic DNA, RNA, or combinations thereof, whether single- or double-stranded) that comprise a nucleotide sequence encoding the amino acid sequence of the polypeptides of the invention. Such polynucleotides are useful for recombinantly expressing the receptor and also for detecting expression of the receptor in cells (*e.g.*, using Northern hybridization and *in situ* hybridization assays). Such polynucleotides also are useful in the design of antisense and other molecules for the suppression of the expression of nGPCR-x in a cultured cell, a tissue, or an animal; for therapeutic purposes; or to provide a model for diseases or conditions characterized by aberrant nGPCR-x expression. Specifically excluded from the definition of polynucleotides of the invention are entire isolated, non-recombinant native chromosomes of host cells. A preferred polynucleotide has a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, which correspond to naturally occurring nGPCR-x sequences. It will be appreciated that numerous other polynucleotide sequences exist that also encode nGPCR-x having the sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, due to the well-known degeneracy of the universal genetic code.

[00059] The invention also provides a purified and isolated polynucleotide comprising a nucleotide sequence that encodes a mammalian polypeptide, wherein the polynucleotide hybridizes to a polynucleotide having the sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or the non-coding strand complementary thereto, under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate; and

(b) washing 2 times for 30 minutes each at 60°C in a wash solution comprising 0.1% SSC, 1% SDS. Polynucleotides that encode a human allelic variant are highly preferred.

- [00060] The present invention relates to molecules which comprise the gene sequences that encode the nGPCRs; constructs and recombinant host cells incorporating the gene sequences; the novel GPCR polypeptides encoded by the gene sequences; antibodies to the polypeptides and homologs; kits employing the polynucleotides and polypeptides, and methods of making and using all of the foregoing. In addition, the present invention relates to homologs of the gene sequences and of the polypeptides and methods of making and using the same.
- [00061] Genomic DNA of the invention comprises the protein-coding region for a polypeptide of the invention and is also intended to include allelic variants thereof. It is widely understood that, for many genes, genomic DNA is transcribed into RNA transcripts that undergo one or more splicing events wherein intron (*i.e.*, non-coding regions) of the transcripts are removed, or "spliced out." RNA transcripts that can be spliced by alternative mechanisms, and therefore be subject to removal of different RNA sequences but still encode a nGPCR-x polypeptide, are referred to in the art as splice variants which are embraced by the invention. Splice variants comprehended by the invention therefore are encoded by the same original genomic DNA sequences but arise from distinct mRNA transcripts. Allelic variants are modified forms of a wild-type gene sequence, the modification resulting from recombination during chromosomal segregation or exposure to conditions which give rise to genetic mutation. Allelic variants, like wild type genes, are naturally occurring sequences (as opposed to non-naturally occurring variants that arise from *in vitro* manipulation).
- [00062] The invention also comprehends cDNA that is obtained through reverse transcription of an RNA polynucleotide encoding nGPCR-x (conventionally followed by second strand synthesis of a complementary strand to provide a double-stranded DNA).
- [00063] Preferred DNA sequences encoding human nGPCR-x polypeptides are selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128. A preferred DNA of the invention comprises a double stranded molecule along with the complementary molecule (the "non-coding strand" or "complement") having a sequence unambiguously deducible from the coding strand according to Watson-Crick base-pairing rules for DNA. Also preferred are other polynucleotides encoding the nGPCR-x polypeptide selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, which differ in sequence from the polynucleotides selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, by virtue of the well-known degeneracy of the universal nuclear genetic code.
- [00064] The invention further embraces other species, preferably mammalian, homologs of the human nGPCR-x DNA. Species homologs, sometimes referred to as "orthologs," in general, share at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, or at least

99% homology with human DNA of the invention. Generally, percent sequence "homology" with respect to polynucleotides of the invention may be calculated as the percentage of nucleotide bases in the candidate sequence that are identical to nucleotides in the nGPCR-x sequence set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity.

[00065] Polynucleotides of the invention permit identification and isolation of polynucleotides encoding related nGPCR-x polypeptides, such as human allelic variants and species homologs, by well-known techniques including Southern and/or Northern hybridization, and polymerase chain reaction (PCR). Examples of related polynucleotides include human and non-human genomic sequences, including allelic variants, as well as polynucleotides encoding polypeptides homologous to nGPCR-x and structurally related polypeptides sharing one or more biological, immunological, and/or physical properties of nGPCR-x. Non-human species genes encoding proteins homologous to nGPCR-x can also be identified by Southern and/or PCR analysis and are useful in animal models for nGPCR-x disorders. Knowledge of the sequence of a human nGPCR-x DNA also makes possible through use of Southern hybridization or polymerase chain reaction (PCR) the identification of genomic DNA sequences encoding nGPCR-x expression control regulatory sequences such as promoters, operators, enhancers, repressors, and the like. Polynucleotides of the invention are also useful in hybridization assays to detect the capacity of cells to express nGPCR-x. Polynucleotides of the invention may also provide a basis for diagnostic methods useful for identifying a genetic alteration(s) in a nGPCR-x locus that underlies a disease state or states, which information is useful both for diagnosis and for selection of therapeutic strategies.

[00066] According to the present invention, the nGPCR-x nucleotide sequences disclosed herein may be used to identify homologs of the nGPCR-x, in other animals, including but not limited to humans and other mammals, and invertebrates. Any of the nucleotide sequences disclosed herein, or any portion thereof, can be used, for example, as probes to screen databases or nucleic acid libraries, such as, for example, genomic or cDNA libraries, to identify homologs, using screening procedures well known to those skilled in the art. Accordingly, homologs having at least 50%, more preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably at least 95%, and most preferably at least 100% homology with nGPCR-x sequences can be identified.

[00067] The disclosure herein of full-length polynucleotides encoding nGPCR-x polypeptides makes readily available to the worker of ordinary skill in the art every possible fragment of the full-length polynucleotide.

[00068] One preferred embodiment of the present invention provides an isolated nucleic acid molecule comprising a sequence homologous sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, and fragments thereof. Another preferred embodiment provides an isolated nucleic acid molecule comprising a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, and fragments thereof.

[00069] As used in the present invention, fragments of nGPCR-x-encoding polynucleotides comprise at least 10, and preferably at least 12, 14, 16, 18, 20, 25, 50, or 75 consecutive nucleotides of a polynucleotide encoding nGPCR-x. Preferably, fragment polynucleotides of the invention comprise sequences unique to the nGPCR-x-encoding polynucleotide sequence, and therefore hybridize under highly stringent or moderately stringent conditions only (*i.e.*, "specifically") to polynucleotides encoding nGPCR-x (or fragments thereof). Polynucleotide fragments of genomic sequences of the invention comprise not only sequences unique to the coding region, but also include fragments of the full-length sequence derived from introns, regulatory regions, and/or other non-translated sequences. Sequences unique to polynucleotides of the invention are recognizable through sequence comparison to other known polynucleotides, and can be identified through use of alignment programs routinely utilized in the art, *e.g.*, those made available in public sequence databases. Such sequences also are recognizable from Southern hybridization analyses to determine the number of fragments of genomic DNA to which a polynucleotide will hybridize. Polynucleotides of the invention can be labeled in a manner that permits their detection, including radioactive, fluorescent, and enzymatic labeling.

[00070] Fragment polynucleotides are particularly useful as probes for detection of full-length or fragments of nGPCR-x polynucleotides. One or more polynucleotides can be included in kits that are used to detect the presence of a polynucleotide encoding nGPCR-x, or used to detect variations in a polynucleotide sequence encoding nGPCR-x.

[00071] The invention also embraces DNAs encoding nGPCR-x polypeptides that hybridize under moderately stringent or high stringency conditions to the non-coding strand, or complement, of the polynucleotides set forth in sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128.

[00072] Exemplary highly stringent hybridization conditions are as follows: hybridization at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% Dextran sulfate, and washing twice for 30 minutes at 60°C in a wash solution comprising 0.1X SSC and 1% SDS. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described Ausubel *et al.* (Eds.), Protocols in Molecular Biology, John Wiley & Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated

based on the length and the percentage of guanosine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, *et al.*, (Eds.), Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989), pp. 9.47 to 9.51.

[00073] With the knowledge of the nucleotide sequence information disclosed in the present invention, one skilled in the art can identify and obtain nucleotide sequences which encode nGPCR-x from different sources (*i.e.*, different tissues or different organisms) through a variety of means well known to the skilled artisan and as disclosed by, for example, Sambrook *et al.*, "Molecular cloning: a laboratory manual", Second Edition, Cold Spring Harbor Press, Cold Spring Harbor, NY (1989), which is incorporated herein by reference in its entirety.

[00074] For example, DNA that encodes nGPCR-x may be obtained by screening of mRNA, cDNA, or genomic DNA with oligonucleotide probes generated from the nGPCR-x gene sequence information provided herein. Probes may be labeled with a detectable group, such as a fluorescent group, a radioactive atom or a chemiluminescent group in accordance with procedures known to the skilled artisan and used in conventional hybridization assays, as described by, for example, Sambrook *et al.*

[00075] A nucleic acid molecule comprising any of the nGPCR-x nucleotide sequences described above can alternatively be synthesized by use of the polymerase chain reaction (PCR) procedure, with the PCR oligonucleotide primers produced from the nucleotide sequences provided herein. See U.S. Patent Numbers 4,683,195 to Mullis *et al.* and 4,683,202 to Mullis. The PCR reaction provides a method for selectively increasing the concentration of a particular nucleic acid sequence even when that sequence has not been previously purified and is present only in a single copy in a particular sample. The method can be used to amplify either single or double-stranded DNA. The essence of the method involves the use of two oligonucleotide probes to serve as primers for the template-dependent, polymerase mediated replication of a desired nucleic acid molecule.

[00076] A wide variety of alternative cloning and *in vitro* amplification methodologies are well known to those skilled in the art. Examples of these techniques are found in, for example, Berger *et al.*, *Guide to Molecular Cloning Techniques*, Methods in Enzymology 152, Academic Press, Inc., San Diego, CA (Berger), which is incorporated herein by reference in its entirety.

[00077] Automated sequencing methods can be used to obtain or verify the nucleotide sequence of nGPCR-x. The nGPCR-x nucleotide sequences of the present invention are believed to be 100% accurate. However, as is known in the art, nucleotide sequence obtained by automated methods may contain some errors. Nucleotide sequences determined by automation are typically at least about 90%, more typically at least about 95% to at least about 99.9% identical

to the actual nucleotide sequence of a given nucleic acid molecule. The actual sequence may be more precisely determined using manual sequencing methods, which are well known in the art. An error in a sequence which results in an insertion or deletion of one or more nucleotides may result in a frame shift in translation such that the predicted amino acid sequence will differ from that which would be predicted from the actual nucleotide sequence of the nucleic acid molecule, starting at the point of the mutation.

[00078] The nucleic acid molecules of the present invention, and fragments derived therefrom, are useful for screening for restriction fragment length polymorphism (RFLP) associated with certain disorders, as well as for genetic mapping.

[00079] The polynucleotide sequence information provided by the invention makes possible large-scale expression of the encoded polypeptide by techniques well known and routinely practiced in the art.

#### Vectors

[00080] Another aspect of the present invention is directed to vectors, or recombinant expression vectors, comprising any of the nucleic acid molecules described above. Vectors are used herein either to amplify DNA or RNA encoding nGPCR-x and/or to express DNA which encodes nGPCR-x. Preferred vectors include, but are not limited to, plasmids, phages, cosmids, episomes, viral particles or viruses, and integratable DNA fragments (*i.e.*, fragments integratable into the host genome by homologous recombination). Preferred viral particles include, but are not limited to, adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses. Preferred expression vectors include, but are not limited to, pcDNA3 (Invitrogen) and pSVL (Pharmacia Biotech). Other expression vectors include, but are not limited to, pSPORT™ vectors, pGEM™ vectors (Promega), pPROEXvectors™ (LTI, Bethesda, MD), Bluescript™ vectors (Stratagene), pQE™ vectors (Qiagen), pSE420™ (Invitrogen), and pYES2™ (Invitrogen).

[00081] Expression constructs preferably comprise GPCR-x-encoding polynucleotides operatively linked to an endogenous or exogenous expression control DNA sequence and a transcription terminator. Expression control DNA sequences include promoters, enhancers, operators, and regulatory element binding sites generally, and are typically selected based on the expression systems in which the expression construct is to be utilized. Preferred promoter and enhancer sequences are generally selected for the ability to increase gene expression, while operator sequences are generally selected for the ability to regulate gene expression. Expression constructs of the invention may also include sequences encoding one or more selectable markers that permit identification of host cells bearing the construct. Expression constructs may also include sequences that facilitate, and preferably promote, homologous recombination in a host

cell. Preferred constructs of the invention also include sequences necessary for replication in a host cell.

[00082] Expression constructs are preferably utilized for production of an encoded protein, but may also be utilized simply to amplify a nGPCR-x-encoding polynucleotide sequence. In preferred embodiments, the vector is an expression vector wherein the polynucleotide of the invention is operatively linked to a polynucleotide comprising an expression control sequence. Autonomously replicating recombinant expression constructs such as plasmid and viral DNA vectors incorporating polynucleotides of the invention are also provided. Preferred expression vectors are replicable DNA constructs in which a DNA sequence encoding nGPCR-x is operably linked or connected to suitable control sequences capable of effecting the expression of the nGPCR-x in a suitable host. DNA regions are operably linked or connected when they are functionally related to each other. For example, a promoter is operably linked or connected to a coding sequence if it controls the transcription of the sequence. Amplification vectors do not require expression control domains, but rather need only the ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants. The need for control sequences in the expression vector will vary depending upon the host selected and the transformation method chosen. Generally, control sequences include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding and sequences which control the termination of transcription and translation.

[00083] Preferred vectors preferably contain a promoter that is recognized by the host organism. The promoter sequences of the present invention may be prokaryotic, eukaryotic or viral. Examples of suitable prokaryotic sequences include the  $P_R$  and  $P_L$  promoters of bacteriophage lambda (The bacteriophage Lambda, Hershey, A. D., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1973), which is incorporated herein by reference in its entirety; Lambda II, Hendrix, R. W., Ed., Cold Spring Harbor Press, Cold Spring Harbor, NY (1980), which is incorporated herein by reference in its entirety); the *trp*, *recA*, heat shock, and *lacZ* promoters of *E. coli* and the SV40 early promoter (Benoist *et al. Nature*, 1981, 290, 304-310, which is incorporated herein by reference in its entirety). Additional promoters include, but are not limited to, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, Rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metallothionein.

[00084] Additional regulatory sequences can also be included in preferred vectors. Preferred examples of suitable regulatory sequences are represented by the Shine-Dalgarno of the



replicase gene of the phage MS-2 and of the gene *cII* of bacteriophage lambda. The Shine-Dalgarno sequence may be directly followed by DNA encoding nGPCR-x and result in the expression of the mature nGPCR-x protein.

[00085] Moreover, suitable expression vectors can include an appropriate marker that allows the screening of the transformed host cells. The transformation of the selected host is carried out using any one of the various techniques well known to the expert in the art and described in Sambrook *et al.*, *supra*.

[00086] An origin of replication can also be provided either by construction of the vector to include an exogenous origin or may be provided by the host cell chromosomal replication mechanism. If the vector is integrated into the host cell chromosome, the latter may be sufficient. Alternatively, rather than using vectors which contain viral origins of replication, one skilled in the art can transform mammalian cells by the method of co-transformation with a selectable marker and nGPCR-x DNA. An example of a suitable marker is dihydrofolate reductase (DHFR) or thymidine kinase (*see*, U.S. Patent No. 4,399,216).

[00087] Nucleotide sequences encoding GPCR-x may be recombined with vector DNA in accordance with conventional techniques, including blunt-ended or staggered-ended termini for ligation, restriction enzyme digestion to provide appropriate termini, filling in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and ligation with appropriate ligases. Techniques for such manipulation are disclosed by Sambrook *et al.*, *supra* and are well known in the art. Methods for construction of mammalian expression vectors are disclosed in, for example, Okayama *et al.*, *Mol. Cell. Biol.*, **1983**, *3*, 280, Cosman *et al.*, *Mol. Immunol.*, **1986**, *23*, 935, Cosman *et al.*, *Nature*, **1984**, *312*, 768, EP-A-0367566, and WO 91/18982, each of which is incorporated herein by reference in its entirety.

#### Host cells

[00088] According to another aspect of the invention, host cells are provided, including prokaryotic and eukaryotic cells, comprising a polynucleotide of the invention (or vector of the invention) in a manner that permits expression of the encoded nGPCR-x polypeptide. Polynucleotides of the invention may be introduced into the host cell as part of a circular plasmid, or as linear DNA comprising an isolated protein coding region or a viral vector. Methods for introducing DNA into the host cell that are well known and routinely practiced in the art include transformation, transfection, electroporation, nuclear injection, or fusion with carriers such as liposomes, micelles, ghost cells, and protoplasts. Expression systems of the invention include bacterial, yeast, fungal, plant, insect, invertebrate, vertebrate, and mammalian cells systems.

[00089] The invention provides host cells that are transformed or transfected (stably or transiently) with polynucleotides of the invention or vectors of the invention. As stated above, such host cells are useful for amplifying the polynucleotides and also for expressing the nGPCR-x polypeptide or fragment thereof encoded by the polynucleotide.

[00090] In still another related embodiment, the invention provides a method for producing a nGPCR-x polypeptide (or fragment thereof) comprising the steps of growing a host cell of the invention in a nutrient medium and isolating the polypeptide or variant thereof from the cell or the medium. Because nGPCR-x is a seven transmembrane receptor, it will be appreciated that, for some applications, such as certain activity assays, the preferable isolation may involve isolation of cell membranes containing the polypeptide embedded therein, whereas for other applications a more complete isolation may be preferable.

[00091] According to some aspects of the present invention, transformed host cells having an expression vector comprising any of the nucleic acid molecules described above are provided. Expression of the nucleotide sequence occurs when the expression vector is introduced into an appropriate host cell. Suitable host cells for expression of the polypeptides of the invention include, but are not limited to, prokaryotes, yeast, and eukaryotes. If a prokaryotic expression vector is employed, then the appropriate host cell would be any prokaryotic cell capable of expressing the cloned sequences. Suitable prokaryotic cells include, but are not limited to, bacteria of the genera *Escherichia*, *Bacillus*, *Salmonella*, *Pseudomonas*, *Streptomyces*, and *Staphylococcus*.

[00092] If an eukaryotic expression vector is employed, then the appropriate host cell would be any eukaryotic cell capable of expressing the cloned sequence. Preferably, eukaryotic cells are cells of higher eukaryotes. Suitable eukaryotic cells include, but are not limited to, non-human mammalian tissue culture cells and human tissue culture cells. Preferred host cells include, but are not limited to, insect cells, HeLa cells, Chinese hamster ovary cells (CHO cells), African green monkey kidney cells (COS cells), human HEK-293 cells, and murine 3T3 fibroblasts. Propagation of such cells in cell culture has become a routine procedure (*see*, Tissue Culture, Academic Press, Kruse and Patterson, eds. (1973), which is incorporated herein by reference in its entirety).

[00093] In addition, a yeast host may be employed as a host cell. Preferred yeast cells include, but are not limited to, the genera *Saccharomyces*, *Pichia*, and *Kluveromyces*. Preferred yeast hosts are *S. cerevisiae* and *P. pastoris*. Preferred yeast vectors can contain an origin of replication sequence from a 2T yeast plasmid, an autonomously replication sequence (ARS), a promoter region, sequences for polyadenylation, sequences for transcription termination, and a

selectable marker gene. Shuttle vectors for replication in both yeast and *E. coli* are also included herein.

[00094] Alternatively, insect cells may be used as host cells. In a preferred embodiment, the polypeptides of the invention are expressed using a baculovirus expression system (*see*, Luckow *et al.*, *Bio/Technology*, **1988**, 6, 47, Baculovirus Expression Vectors: A Laboratory Manual, O'Rielly *et al.* (Eds.), W.H. Freeman and Company, New York, **1992**, and U.S. Patent No. 4,879,236, each of which is incorporated herein by reference in its entirety). In addition, the MAXBAC™ complete baculovirus expression system (Invitrogen) can, for example, be used for production in insect cells.

[00095] Host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with nGPCR-x. Host cells of the invention are also useful in methods for the large-scale production of nGPCR-x polypeptides wherein the cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells, or from the medium in which the cells are grown, by purification methods known in the art, *e.g.*, conventional chromatographic methods including immunoaffinity chromatography, receptor affinity chromatography, hydrophobic interaction chromatography, lectin affinity chromatography, size exclusion filtration, cation or anion exchange chromatography, high pressure liquid chromatography (HPLC), reverse phase HPLC, and the like. Still other methods of purification include those methods wherein the desired protein is expressed and purified as a fusion protein having a specific tag, label, or chelating moiety that is recognized by a specific binding partner or agent. The purified protein can be cleaved to yield the desired protein, or can be left as an intact fusion protein. Cleavage of the fusion component may produce a form of the desired protein having additional amino acid residues as a result of the cleavage process.

[00096] Knowledge of nGPCR-x DNA sequences allows for modification of cells to permit, or increase, expression of endogenous nGPCR-x. Cells can be modified (*e.g.*, by homologous recombination) to provide increased expression by replacing, in whole or in part, the naturally occurring nGPCR-x promoter with all or part of a heterologous promoter so that the cells express nGPCR-x at higher levels. The heterologous promoter is inserted in such a manner that it is operatively linked to endogenous nGPCR-x encoding sequences. (See, for example, PCT International Publication No. WO 94/12650, PCT International Publication No. WO 92/20808, and PCT International Publication No. WO 91/09955.) It is also contemplated that, in addition to heterologous promoter DNA, amplifiable marker DNA (*e.g.*, *ada*, *dhfr*, and the multifunctional CAD gene which encodes carbamoyl phosphate synthase, aspartate transcarbamylase, and dihydroorotase) and/or intron DNA may be inserted along with the heterologous promoter DNA. If linked to the nGPCR-x coding sequence, amplification of the

marker DNA by standard selection methods results in co-amplification of the nGPCR-x coding sequences in the cells.

#### **Knock-outs**

[00097] The DNA sequence information provided by the present invention also makes possible the development (*e.g.*, by homologous recombination or "knock-out" strategies; see Capecchi, *Science* 244:1288-1292 (1989), which is incorporated herein by reference) of animals that fail to express functional nGPCR-x or that express a variant of nGPCR-x. Such animals (especially small laboratory animals such as rats, rabbits, and mice) are useful as models for studying their *vivo* activities of nGPCR-x and modulators of nGPCR-x.

#### **Antisense**

[00098] Also made available by the invention are anti-sense polynucleotides that recognize and hybridize to polynucleotides encoding nGPCR-x. Full-length and fragment anti-sense polynucleotides are provided. Fragment antisense molecules of the invention include (i) those that specifically recognize and hybridize to nGPCR-x RNA (as determined by sequence comparison of DNA encoding nGPCR-x to DNA encoding other known molecules). Identification of sequences unique to nGPCR-x encoding polynucleotides can be deduced through use of any publicly available sequence database, and/or through use of commercially available sequence comparison programs. After identification of the desired sequences, isolation through restriction digestion or amplification using any of the various polymerase chain reaction techniques well known in the art can be performed. Anti-sense polynucleotides are particularly relevant to regulating expression of nGPCR-x by those cells expressing nGPCR-x mRNA.

[00099] Antisense nucleic acids (preferably 10 to 30 base-pair oligonucleotides) capable of specifically binding to nGPCR-x expression control sequences or nGPCR-x RNA are introduced into cells (*e.g.*, by a viral vector or colloidal dispersion system such as a liposome). The antisense nucleic acid binds to the nGPCR-x target nucleotide sequence in the cell and prevents transcription and/or translation of the target sequence. Phosphorothioate and methylphosphonate antisense oligonucleotides are specifically contemplated for therapeutic use by the invention. The antisense oligonucleotides may be further modified by adding poly-L-lysine, transferrin polylysine, or cholesterol moieties at their 5' end. Suppression of nGPCR-x expression at either the transcriptional or translational level is useful to generate cellular or animal models for diseases/conditions characterized by aberrant nGPCR-x expression.

[000100] Antisense oligonucleotides, or fragments of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or sequences complementary or homologous thereto, derived from the nucleotide sequences of the present invention encoding nGPCR-x are

useful as diagnostic tools for probing gene expression in various tissues. For example, tissue can be probed *in situ* with oligonucleotide probes carrying detectable groups by conventional autoradiography techniques to investigate native expression of this enzyme or pathological conditions relating thereto. Antisense oligonucleotides are preferably directed to regulatory regions of sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or mRNA corresponding thereto, including, but not limited to, the initiation codon, TATA box, enhancer sequences, and the like.

### Transcription factors

[000101] The nGPCR-x sequences taught in the present invention facilitate the design of novel transcription factors for modulating nGPCR-x expression in native cells and animals, and cells transformed or transfected with nGPCR-x polynucleotides. For example, the Cys<sub>2</sub>-His<sub>2</sub> zinc finger proteins, which bind DNA via their zinc finger domains, have been shown to be amenable to structural changes that lead to the recognition of different target sequences. These artificial zinc finger proteins recognize specific target sites with high affinity and low dissociation constants, and are able to act as gene switches to modulate gene expression. Knowledge of the particular nGPCR-x target sequence of the present invention facilitates the engineering of zinc finger proteins specific for the target sequence using known methods such as a combination of structure-based modeling and screening of phage display libraries (Segal *et al.*, Proc. Natl. Acad. Sci. (USA) 96:2758-2763 (1999); Liu *et al.*, Proc. Natl. Acad. Sci. (USA) 94:5525-5530 (1997); Greisman *et al.*, Science 275:657-661 (1997); Choo *et al.*, J. Mol. Biol. 273:525-532 (1997)). Each zinc finger domain usually recognizes three or more base pairs. Since a recognition sequence of 18 base pairs is generally sufficient in length to render it unique in any known genome, a zinc finger protein consisting of 6 tandem repeats of zinc fingers would be expected to ensure specificity for a particular sequence (Segal *et al.*) The artificial zinc finger repeats, designed based on nGPCR-x sequences, are fused to activation or repression domains to promote or suppress nGPCR-x expression (Liu *et al.*) Alternatively, the zinc finger domains can be fused to the TATA box-binding factor (TBP) with varying lengths of linker region between the zinc finger peptide and the TBP to create either transcriptional activators or repressors (Kim *et al.*, Proc. Natl. Acad. Sci. (USA) 94:3616-3620 (1997)). Such proteins and polynucleotides that encode them, have utility for modulating nGPCR-x expression *in vivo* in both native cells, animals and humans; and/or cells transfected with nGPCR-x-encoding sequences. The novel transcription factor can be delivered to the target cells by transfecting constructs that express the transcription factor (gene therapy), or by introducing the protein. Engineered zinc finger proteins can also be designed to bind RNA sequences for use in therapeutics as alternatives to antisense or catalytic RNA methods (McColl *et al.*, Proc. Natl. Acad. Sci. (USA) 96:9521-9526

(1997); Wu *et al.*, Proc. Natl. Acad. Sci. (USA) 92:344-348 (1995)). The present invention contemplates methods of designing such transcription factors based on the gene sequence of the invention, as well as customized zinc finger proteins, that are useful to modulate nGPCR-x expression in cells (native or transformed) whose genetic complement includes these sequences.

### **Polypeptides**

- [000102] The invention also provides purified and isolated mammalian nGPCR-x polypeptides encoded by a polynucleotide of the invention. Presently preferred is a human nGPCR-x polypeptide comprising the amino acid sequence set out in sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, or fragments thereof comprising an epitope specific to the polypeptide. By "epitope specific to" is meant a portion of the nGPCR receptor that is recognizable by an antibody that is specific for the nGPCR, as defined in detail below.
- [000103] Although the sequences provided are particular human sequences, the invention is intended to include within its scope other human allelic variants; non-human mammalian forms of nGPCR-x, and other vertebrate forms of nGPCR-x.
- [000104] It will be appreciated that extracellular epitopes are particularly useful for generating and screening for antibodies and other binding compounds that bind to receptors such as nGPCR-x. Thus, in another preferred embodiment, the invention provides a purified and isolated polypeptide comprising at least one extracellular domain (*e.g.*, the N-terminal extracellular domain or one of the three extracellular loops) of nGPCR-x. Purified and isolated polypeptides comprising the N-terminal extracellular domain of nGPCR-x are highly preferred. Also preferred is a purified and isolated polypeptide comprising a nGPCR-x fragment selected from the group consisting of the N-terminal extracellular domain of nGPCR-x, transmembrane domains of nGPCR-x, an extracellular loop connecting transmembrane domains of nGPCR-x, an intracellular loop connecting transmembrane domains of nGPCR-x, the C-terminal cytoplasmic region of nGPCR-x, and fusions thereof. Such fragments may be continuous portions of the native receptor. However, it will also be appreciated that knowledge of the nGPCR-x gene and protein sequences as provided herein permits recombining of various domains that are not contiguous in the native protein. Using a FORTRAN computer program called "tmrest.all" [Parodi *et al.*, Comput. Appl. Biosci. 5:527-535 (1994)], nGPCR-x was shown to contain transmembrane-spanning domains.
- [000105] The invention also embraces polypeptides that have at least 99%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55% or at least 50% identity and/or homology to the preferred polypeptide of the invention. Percent amino acid sequence "identity" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence

that are identical with the residues in the nGPCR-x sequence after aligning both sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent sequence "homology" with respect to the preferred polypeptide of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the nGPCR-x sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity.

[000106] In one aspect, percent homology is calculated as the percentage of amino acid residues in the smaller of two sequences which align with identical amino acid residue in the sequence being compared, when four gaps in a length of 100 amino acids may be introduced to maximize alignment (Dayhoff, in Atlas of Protein Sequence and Structure, Vol. 5, p. 124, National Biochemical Research Foundation, Washington, D.C. (1972), incorporated herein by reference).

[000107] Polypeptides of the invention may be isolated from natural cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host cells of the invention. Use of mammalian host cells is expected to provide for such post-translational modifications (*e.g.*, glycosylation, truncation, lipidation, and phosphorylation) as may be needed to confer optimal biological activity on recombinant expression products of the invention. Glycosylated and non-glycosylated forms of nGPCR-x polypeptides are embraced by the invention.

[000108] The invention also embraces variant (or analog) nGPCR-x polypeptides. In one example, insertion variants are provided wherein one or more amino acid residues supplement a nGPCR-x amino acid sequence. Insertions may be located at either or both termini of the protein, or may be positioned within internal regions of the nGPCR-x amino acid sequence. Insertional variants with additional residues at either or both termini can include, for example, fusion proteins and proteins including amino acid tags or labels.

[000109] Insertion variants include nGPCR-x polypeptides wherein one or more amino acid residues are added to a nGPCR-x acid sequence or to a biologically active fragment thereof.

[000110] Variant products of the invention also include mature nGPCR-x products, *i.e.*, nGPCR-x products wherein leader or signal sequences are removed, with additional amino terminal residues. The additional amino terminal residues may be derived from another protein, or may include one or more residues that are not identifiable as being derived from specific proteins. nGPCR-x products with an additional methionine residue at position -1 (Met<sup>-1</sup>-nGPCR-x) are contemplated, as are variants with additional methionine and lysine residues at positions -2 and -1 (Met<sup>-2</sup>-Lys<sup>-1</sup>-nGPCR-x). Variants of nGPCR-x with additional Met, Met-Lys, Lys residues

(or one or more basic residues in general) are particularly useful for enhanced recombinant protein production in bacterial host cells.

[000111] The invention also embraces nGPCR-x variants having additional amino acid residues that result from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as part of a glutathione-S-transferase (GST) fusion product provides the desired polypeptide having an additional glycine residue at position-1 after cleavage of the GST component from the desired polypeptide. Variants that result from expression in other vector systems are also contemplated.

[000112] Insertional variants also include fusion proteins wherein the amino terminus and/or the carboxy terminus of nGPCR-x is/are fused to another polypeptide.

[000113] In another aspect, the invention provides deletion variants wherein one or more amino acid residues in a nGPCR-x polypeptide are removed. Deletions can be effected at one or both termini of the nGPCR-x polypeptide, or with removal of one or more non-terminal amino acid residues of nGPCR-x. Deletion variants, therefore, include all fragments of a nGPCR-x polypeptide.

[000114] The invention also embraces polypeptide fragments of sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, wherein the fragments maintain biological (*e.g.*, ligand binding and/or intracellular signaling) immunological properties of a nGPCR-x polypeptide.

[000115] In one preferred embodiment of the invention, an isolated nucleic acid molecule comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, and fragments thereof, wherein the nucleic acid molecule encoding at least a portion of nGPCR-x. In a more preferred embodiment, the isolated nucleic acid molecule comprises a sequence that encodes a polypeptide comprising sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, and fragments thereof.

[000116] As used in the present invention, polypeptide fragments comprise at least 5, 10, 15, 20, 25, 30, 35, or 40 consecutive amino acids of sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257. Preferred polypeptide fragments display antigenic properties unique to, or specific for, human nGPCR-x and its allelic and species homologs. Fragments of the invention having the desired biological and immunological properties can be prepared by any of the methods well known and routinely practiced in the art.

[000117] In still another aspect, the invention provides substitution variants of nGPCR-x polypeptides. Substitution variants include those polypeptides wherein one or more amino acid residues of a nGPCR-x polypeptide are removed and replaced with alternative residues. In one



aspect, the substitutions are conservative in nature; however, the invention embraces substitutions that are also non-conservative. Conservative substitutions for this purpose may be defined as set out in Tables 2, 3, or 4 below.

[000118] Variant polypeptides include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Amino acids can be classified according to physical properties and contribution to secondary and tertiary protein structure. A conservative substitution is recognized in the art as a substitution of one amino acid for another amino acid that has similar properties. Exemplary conservative substitutions are set out in Table 2 (from WO 97/09433, page 10, published March 13, 1997 (PCT/GB96/02197, filed 9/6/96), immediately below.

Table 2

## Conservative Substitutions I

<u>SIDE CHAIN CHARACTERISTIC</u>	<u>AMINO ACID</u>
Aliphatic	
Non-polar	G A P I L V
Polar - uncharged	C S T M N Q
Polar - charged	D E K R
Aromatic	H F W Y
Other	N Q D E

[000119] Alternatively, conservative amino acids can be grouped as described in Lehninger, [Biochemistry, Second Edition; Worth Publishers, Inc. NY, NY (1975), pp.71-77] as set out in Table 3, below.

Table 3

## Conservative Substitutions II

<u>SIDE CHAIN CHARACTERISTIC</u>	<u>AMINO ACID</u>
Non-polar (hydrophobic)	
A. Aliphatic:	A L I V P
B. Aromatic:	F W
C. Sulfur-containing:	M
D. Borderline:	G
Uncharged-polar	
A. Hydroxyl:	S T Y
B. Amides:	N Q
C. Sulfhydryl:	C
D. Borderline:	G
Positively Charged (Basic):	K R H
Negatively Charged (Acidic):	D E

[000120] As still another alternative, exemplary conservative substitutions are set out in Table 4, below.

Table 4

## Conservative Substitutions III

Original Residue	Exemplary Substitution
Ala (A)	Val, Leu, Ile
Arg (R)	Lys, Gln, Asn
Asn (N)	Gln, His, Lys, Arg
Asp (D)	Glu
Cys (C)	Ser
Gln (Q)	Asn
Glu (E)	Asp
His (H)	Asn, Gln, Lys, Arg
Ile (I)	Leu, Val, Met, Ala, Phe,
Leu (L)	Ile, Val, Met, Ala, Phe
Lys (K)	Arg, Gln, Asn
Met (M)	Leu, Phe, Ile
Phe (F)	Leu, Val, Ile, Ala
Pro (P)	Gly
Ser (S)	Thr
Thr (T)	Ser
Trp (W)	Tyr
Tyr (Y)	Trp, Phe, Thr, Ser
Val (V)	Ile, Leu, Met, Phe, Ala

[000121] It should be understood that the definition of polypeptides of the invention is intended to include polypeptides bearing modifications other than insertion, deletion, or substitution of amino acid residues. By way of example, the modifications may be covalent in nature, and include for example, chemical bonding with polymers, lipids, other organic, and inorganic moieties. Such derivatives may be prepared to increase circulating half-life of a polypeptide, or may be designed to improve the targeting capacity of the polypeptide for desired cells, tissues, or organs. Similarly, the invention further embraces nGPCR-x polypeptides that have been covalently modified to include one or more water-soluble polymer attachments such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

[000122] In a related embodiment, the present invention provides compositions comprising purified polypeptides of the invention. Preferred compositions comprise, in addition to the polypeptide of the invention, a pharmaceutically acceptable (*i.e.*, sterile and non-toxic) liquid, semisolid, or solid diluent that serves as a pharmaceutical vehicle, excipient, or medium. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, water, saline solutions, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and

propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, glycerol, calcium phosphate, mineral oil, and cocoa butter.

[000123] Variants that display ligand binding properties of native nGPCR-x and are expressed at higher levels, as well as variants that provide for constitutively active receptors, are particularly useful in assays of the invention; the variants are also useful in assays of the invention and in providing cellular, tissue and animal models of diseases/conditions characterized by aberrant nGPCR-x activity.

[000124] The G protein-coupled receptor functions through a specific heterotrimeric guanine-nucleotide-binding regulatory protein (G-protein) coupled to the intracellular portion of the G protein-coupled receptor molecule. Accordingly, the G protein-coupled receptor has a specific affinity to G protein. G proteins specifically bind to guanine nucleotides. Isolation of G proteins provides a means to isolate guanine nucleotides. G proteins may be isolated using commercially available anti-G protein antibodies or isolated G protein-coupled receptors. Similarly, G proteins may be detected in a sample isolated using commercially available detectable anti-G protein antibodies or isolated G protein-coupled receptors.

[000125] According to the present invention, the isolated nGPCR-x proteins of the present invention are useful to isolate and purify G proteins from samples such as cell lysates. Example 15 below sets forth an example of isolation of G proteins using isolated nGPCR-x proteins. Such methodology may be used in place of the use of commercially available anti-G protein antibodies which are used to isolate G proteins. Moreover, G proteins may be detected using nGPCR-x proteins in place of commercially available detectable anti-G protein antibodies. Since nGPCR-x proteins specifically bind to G proteins, they can be employed in any specific use where G protein specific affinity is required such as those uses where commercially available anti-G protein antibodies are employed.

#### **Antibodies**

[000126] Also comprehended by the present invention are antibodies (*e.g.*, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, bifunctional/bispecific antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) specific for nGPCR-x or fragments thereof. Preferred antibodies of the invention are human antibodies that are produced and identified according to methods described in WO93/11236, published June 20, 1993, which is incorporated herein by reference in its entirety. Antibody fragments, including Fab, Fab', F(ab')<sub>2</sub>, and F<sub>v</sub>, are also provided by the invention. The term "specific for," when used to describe antibodies of the invention, indicates that the variable regions of the antibodies of the

invention recognize and bind nGPCR-x polypeptides exclusively (*i.e.*, are able to distinguish nGPCR-x polypeptides from other known GPCR polypeptides by virtue of measurable differences in binding affinity, despite the possible existence of localized sequence identity, homology, or similarity between nGPCR-x and such polypeptides). It will be understood that specific antibodies may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and, in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see Harlow *et al.* (Eds.), Antibodies A Laboratory Manual; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the nGPCR-x polypeptides of the invention are also contemplated, provided that the antibodies are specific for nGPCR-x polypeptides. Antibodies of the invention can be produced using any method well known and routinely practiced in the art.

[000127] The invention provides an antibody that is specific for the nGPCR-x of the invention. Antibody specificity is described in greater detail below. However, it should be emphasized that antibodies that can be generated from polypeptides that have previously been described in the literature and that are capable of fortuitously cross-reacting with nGPCR-x (*e.g.*, due to the fortuitous existence of a similar epitope in both polypeptides) are considered "cross-reactive" antibodies. Such cross-reactive antibodies are not antibodies that are "specific" for nGPCR-x. The determination of whether an antibody is specific for nGPCR-x or is cross-reactive with another known receptor is made using any of several assays, such as Western blotting assays, that are well known in the art. For identifying cells that express nGPCR-x and also for modulating nGPCR-x-ligand binding activity, antibodies that specifically bind to an extracellular epitope of the nGPCR-x are preferred.

[000128] In one preferred variation, the invention provides monoclonal antibodies. Hybridomas that produce such antibodies also are intended as aspects of the invention. In yet another variation, the invention provides a humanized antibody. Humanized antibodies are useful for *in vivo* therapeutic indications.

[000129] In another variation, the invention provides a cell-free composition comprising polyclonal antibodies, wherein at least one of the antibodies is an antibody of the invention specific for nGPCR-x. Antisera isolated from an animal is an exemplary composition, as is a composition comprising an antibody fraction of an antisera that has been resuspended in water or in another diluent, excipient, or carrier.

- [000130] In still another related embodiment, the invention provides an anti-idiotypic antibody specific for an antibody that is specific for nGPCR-x.
- [000131] It is well known that antibodies contain relatively small antigen binding domains that can be isolated chemically or by recombinant techniques. Such domains are useful nGPCR-x binding molecules themselves, and also may be reintroduced into human antibodies, or fused to toxins or other polypeptides. Thus, in still another embodiment, the invention provides a polypeptide comprising a fragment of a nGPCR-x-specific antibody, wherein the fragment and the polypeptide bind to the nGPCR-x. By way of non-limiting example, the invention provides polypeptides that are single chain antibodies and CDR-grafted antibodies.
- [000132] Non-human antibodies may be humanized by any of the methods known in the art. In one method, the non-human CDRs are inserted into a human antibody or consensus antibody framework sequence. Further changes can then be introduced into the antibody framework to modulate affinity or immunogenicity.
- [000133] Antibodies of the invention are useful for, *e.g.*, therapeutic purposes (by modulating activity of nGPCR-x), diagnostic purposes to detect or quantitate nGPCR-x, and purification of nGPCR-x. Kits comprising an antibody of the invention for any of the purposes described herein are also comprehended. In general, a kit of the invention also includes a control antigen for which the antibody is immunospecific.

#### Compositions

- [000134] Mutations in the nGPCR-x gene that result in loss of normal function of the nGPCR-x gene product underlie nGPCR-x-related human disease states. The invention comprehends gene therapy to restore nGPCR-x activity to treat those disease states. Delivery of a functional nGPCR-x gene to appropriate cells is effected *ex vivo*, *in situ*, or *in vivo* by use of vectors, and more particularly viral vectors (*e.g.*, adenovirus, adeno-associated virus, or a retrovirus), or *ex vivo* by use of physical DNA transfer methods (*e.g.*, liposomes or chemical treatments). See, for example, Anderson, *Nature*, supplement to vol. 392, no. 6679, pp.25-20 (1998). For additional reviews of gene therapy technology see Friedmann, *Science*, 244: 1275-1281 (1989); Verma, *Scientific American*: 68-84 (1990); and Miller, *Nature*, 357: 455-460 (1992). Alternatively, it is contemplated that in other human disease states, preventing the expression of, or inhibiting the activity of, nGPCR-x will be useful in treating disease states. It is contemplated that antisense therapy or gene therapy could be applied to negatively regulate the expression of nGPCR-x.
- [000135] Another aspect of the present invention is directed to compositions, including pharmaceutical compositions, comprising any of the nucleic acid molecules or recombinant expression vectors described above and an acceptable carrier or diluent. Preferably, the carrier or diluent is pharmaceutically acceptable. Suitable carriers are described in the most recent

edition of *Remington's Pharmaceutical Sciences*, A. Osol, a standard reference text in this field, which is incorporated herein by reference in its entirety. Preferred examples of such carriers or diluents include, but are not limited to, water, saline, Ringer's solution, dextrose solution, and 5% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils may also be used. The formulations are sterilized by commonly used techniques.

[000136] Also within the scope of the invention are compositions comprising polypeptides, polynucleotides, or antibodies of the invention that have been formulated with, *e.g.*, a pharmaceutically acceptable carrier.

[000137] The invention also provides methods of using antibodies of the invention. For example, the invention provides a method for modulating ligand binding of a nGPCR-x comprising the step of contacting the nGPCR-x with an antibody specific for the nGPCR-x, under conditions wherein the antibody binds the receptor.

[000138] As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. GPCRs that may be expressed in the brain, such as nGPCR-x, provide an indication that aberrant nGPCR-x signaling activity may correlate with one or more neurological or psychological disorders. The invention also provides a method for treating a neurological or psychiatric disorder comprising the step of administering to a mammal in need of such treatment an amount of an antibody-like polypeptide of the invention that is sufficient to modulate ligand binding to a nGPCR-x in neurons of the mammal. nGPCR-x may also be expressed in other tissues, including but not limited to, peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, thyroid gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon, muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons, cerebellum, caudate nucleus, and medulla.

#### Kits

[000139] The present invention is also directed to kits, including pharmaceutical kits. The kits can comprise any of the nucleic acid molecules described above, any of the polypeptides described above, or any antibody which binds to a polypeptide of the invention as described above, as well as a negative control. The kit preferably comprises additional components, such as, for example, instructions, solid support, reagents helpful for quantification, and the like.

[000140] In another aspect, the invention features methods for detection of a polypeptide in a sample as a diagnostic tool for diseases or disorders, wherein the method comprises the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a polypeptide having sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, said probe comprising the nucleic acid

sequence encoding the polypeptide, fragments thereof, and the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

[000141] In preferred embodiments of the invention, the disease is selected from the group consisting of thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Crohn's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); and sexual dysfunction, among others.

[000142] Kits may be designed to detect either expression of polynucleotides encoding nGPCR-x expressed in the brain or the nGPCR-x proteins themselves in order to identify tissue as being neurological. For example, oligonucleotide hybridization kits can be provided which include a container having an oligonucleotide probe specific for the nGPCR-x-specific DNA and optionally, containers with positive and negative controls and/or instructions. Similarly, PCR kits can be provided which include a container having primers specific for the nGPCR-x-specific sequences, DNA and optionally, containers with size markers, positive and negative controls and/or instructions.

[000143] Hybridization conditions should be such that hybridization occurs only with the genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having 1 or 2 mismatches out of 20 contiguous nucleotides. Such conditions are defined supra.

[000144] The diseases for which detection of genes in a sample could be diagnostic include diseases in which nucleic acid (DNA and/or RNA) is amplified in comparison to normal cells.

By "amplification" is meant increased numbers of DNA or RNA in a cell compared with normal cells.

[000145] The diseases that could be diagnosed by detection of nucleic acid in a sample preferably include central nervous system and metabolic diseases. The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

[000146] Alternatively, immunoassay kits can be provided which have containers container having antibodies specific for the nGPCR-x-protein and optionally, containers with positive and negative controls and/or instructions.

[000147] Kits may also be provided useful in the identification of GPCR binding partners such as natural ligands or modulators (agonists or antagonists). Substances useful for treatment of disorders or diseases preferably show positive results in one or more *in vitro* assays for an activity corresponding to treatment of the disease or disorder in question. Substances that modulate the activity of the polypeptides preferably include, but are not limited to, antisense oligonucleotides, agonists and antagonists, and inhibitors of protein kinases.

#### **Methods of inducing immune response**

[000148] Another aspect of the present invention is directed to methods of inducing an immune response in a mammal against a polypeptide of the invention by administering to the mammal an amount of the polypeptide sufficient to induce an immune response. The amount will be dependent on the animal species, size of the animal, and the like but can be determined by those skilled in the art.

#### **Methods of identifying ligands**

[000149] The invention also provides assays to identify compounds that bind nGPCR-x. One such assay comprises the steps of: (a) contacting a composition comprising a nGPCR-x with a compound suspected of binding nGPCR-x; and (b) measuring binding between the compound and nGPCR-x. In one variation, the composition comprises a cell expressing nGPCR-x on its surface. In another variation, isolated nGPCR-x or cell membranes comprising nGPCR-x are employed. The binding may be measured directly, *e.g.*, by using a labeled compound, or may be measured indirectly by several techniques, including measuring intracellular signaling of nGPCR-x induced by the compound (or measuring changes in the level of nGPCR-x signaling). Following steps (a) and (b), compounds identified as binding nGPCR-x may be tested in other



assays including, but not limited to, *in vivo* models, to confirm or quantitate binding to nGPCR-x.

[000150] Specific binding molecules, including natural ligands and synthetic compounds, can be identified or developed using isolated or recombinant nGPCR-x products, nGPCR-x variants, or preferably, cells expressing such products. Binding partners are useful for purifying nGPCR-x products and detection or quantification of nGPCR-x products in fluid and tissue samples using known immunological procedures. Binding molecules are also manifestly useful in modulating (*i.e.*, blocking, inhibiting or stimulating) biological activities of nGPCR-x, especially those activities involved in signal transduction.

[000151] The DNA and amino acid sequence information provided by the present invention also makes possible identification of binding partner compounds with which a nGPCR-x polypeptide or polynucleotide will interact. Methods to identify binding partner compounds include solution assays, *in vitro* assays wherein nGPCR-x polypeptides are immobilized, and cell-based assays. Identification of binding partner compounds of nGPCR-x polypeptides provides candidates for therapeutic or prophylactic intervention in pathologies associated with nGPCR-x normal and aberrant biological activity.

[000152] The invention includes several assay systems for identifying nGPCR-x binding partners. In solution assays, methods of the invention comprise the steps of (a) contacting a nGPCR-x polypeptide with one or more candidate binding partner compounds and (b) identifying the compounds that bind to the nGPCR-x polypeptide. Identification of the compounds that bind the nGPCR-x polypeptide can be achieved by isolating the nGPCR-x polypeptide/binding partner complex, and separating the binding partner compound from the nGPCR-x polypeptide. An additional step of characterizing the physical, biological, and/or biochemical properties of the binding partner compound is also comprehended in another embodiment of the invention, wherein compounds identified as binding nGPCR-x may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate binding to nGPCR-x. In one aspect, the nGPCR-x polypeptide/binding partner complex is isolated using an antibody immunospecific for either the nGPCR-x polypeptide or the candidate binding partner compound.

[000153] In still other embodiments, either the nGPCR-x polypeptide or the candidate binding partner compound comprises a label or tag that facilitates its isolation, and methods of the invention to identify binding partner compounds include a step of isolating the nGPCR-x polypeptide/binding partner complex through interaction with the label or tag. An exemplary tag of this type is a poly-histidine sequence, generally around six histidine residues, that permits isolation of a compound so labeled using nickel chelation. Other labels and tags, such as the

FLAG<sup>®</sup> tag (Eastman Kodak, Rochester, NY), well known and routinely used in the art, are embraced by the invention.

[000154] In one variation of an *in vitro* assay, the invention provides a method comprising the steps of (a) contacting an immobilized nGPCR-x polypeptide with a candidate binding partner compound and (b) detecting binding of the candidate compound to the nGPCR-x polypeptide. In an alternative embodiment, the candidate binding partner compound is immobilized and binding of nGPCR-x is detected. Immobilization is accomplished using any of the methods well known in the art, including covalent bonding to a support, a bead, or a chromatographic resin, as well as non-covalent, high affinity interactions such as antibody binding, or use of streptavidin/biotin binding wherein the immobilized compound includes a biotin moiety. Detection of binding can be accomplished (i) using a radioactive label on the compound that is not immobilized, (ii) using of a fluorescent label on the non-immobilized compound, (iii) using an antibody immunospecific for the non-immobilized compound, (iv) using a label on the non-immobilized compound that excites a fluorescent support to which the immobilized compound is attached, as well as other techniques well known and routinely practiced in the art.

[000155] The invention also provides cell-based assays to identify binding partner compounds of a nGPCR-x polypeptide. In one embodiment, the invention provides a method comprising the steps of contacting a nGPCR-x polypeptide expressed on the surface of a cell with a candidate binding partner compound and detecting binding of the candidate binding partner compound to the nGPCR-x polypeptide. In a preferred embodiment, the detection comprises detecting a calcium flux or other physiological event in the cell caused by the binding of the molecule.

[000156] Another aspect of the present invention is directed to methods of identifying compounds that bind to either nGPCR-x or nucleic acid molecules encoding nGPCR-x, comprising contacting nGPCR-x, or a nucleic acid molecule encoding the same, with a compound, and determining whether the compound binds nGPCR-x or a nucleic acid molecule encoding the same. Binding can be determined by binding assays which are well known to the skilled artisan, including, but not limited to, gel-shift assays, Western blots, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, ELISA, and the like, which are described in, for example, *Current Protocols in Molecular Biology*, 1999, John Wiley & Sons, NY, which is incorporated herein by reference in its entirety. The compounds to be screened include (which may include compounds which are suspected to bind nGPCR-x, or a nucleic acid molecule encoding the same), but are not limited to, extracellular, intracellular, biologic or chemical origin. The methods of the invention also embrace ligands, especially neuropeptides, that are attached to a label, such as a radiolabel (e.g., <sup>125</sup>I, <sup>35</sup>S, <sup>32</sup>P, <sup>33</sup>P, <sup>3</sup>H), a

fluorescence label, a chemiluminescent label, an enzymic label and an immunogenic label. Modulators falling within the scope of the invention include, but are not limited to, non-peptide molecules such as non-peptide mimetics, non-peptide allosteric effectors, and peptides. The nGPCR-x polypeptide or polynucleotide employed in such a test may either be free in solution, attached to a solid support, borne on a cell surface or located intracellularly or associated with a portion of a cell. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

[000157] In another embodiment of the invention, high throughput screening for compounds having suitable binding affinity to nGPCR-x is employed. Briefly, large numbers of different test compounds are synthesized on a solid substrate. The peptide test compounds are contacted with nGPCR-x and washed. Bound nGPCR-x is then detected by methods well known in the art. Purified polypeptides of the invention can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the protein and immobilize it on the solid support.

[000158] Generally, an expressed nGPCR-x can be used for HTS binding assays in conjunction with its defined ligand, in this case the corresponding neuropeptide that activates it. The identified peptide is labeled with a suitable radioisotope, including, but not limited to,  $^{125}\text{I}$ ,  $^3\text{H}$ ,  $^{35}\text{S}$  or  $^{32}\text{P}$ , by methods that are well known to those skilled in the art. Alternatively, the peptides may be labeled by well-known methods with a suitable fluorescent derivative (Baindur *et al.*, *Drug Dev. Res.*, **1994**, 33, 373-398; Rogers, *Drug Discovery Today*, **1997**, 2, 156-160). Radioactive ligand specifically bound to the receptor in membrane preparations made from the cell line expressing the recombinant protein can be detected in HTS assays in one of several standard ways, including filtration of the receptor-ligand complex to separate bound ligand from unbound ligand (Williams, *Med. Res. Rev.*, **1991**, 11, 147-184; Sweetnam *et al.*, *J. Natural Products*, **1993**, 56, 441-455). Alternative methods include a scintillation proximity assay (SPA) or a FlashPlate format in which such separation is unnecessary (Nakayama, *Cur. Opinion Drug Disc. Dev.*, **1998**, 1, 85-91 Bossé *et al.*, *J. Biomolecular Screening*, **1998**, 3, 285-292.). Binding of fluorescent ligands can be detected in various ways, including fluorescence energy transfer (FRET), direct spectrophotofluorometric analysis of bound ligand, or fluorescence polarization (Rogers, *Drug Discovery Today*, **1997**, 2, 156-160; Hill, *Cur. Opinion Drug Disc. Dev.*, **1998**, 1, 92-97).

[000159] Other assays may be used to identify specific ligands of a nGPCR-x receptor, including assays that identify ligands of the target protein through measuring direct binding of test ligands

to the target protein, as well as assays that identify ligands of target proteins through affinity ultrafiltration with ion spray mass spectroscopy/HPLC methods or other physical and analytical methods. Alternatively, such binding interactions are evaluated indirectly using the yeast two-hybrid system described in Fields *et al.*, Nature, 340:245-246 (1989), and Fieldset *al.*, Trends in Genetics, 10:286-292 (1994), both of which are incorporated herein by reference. The two-hybrid system is a genetic assay for detecting interactions between two proteins or polypeptides. It can be used to identify proteins that bind to a known protein of interest, or to delineate domains or residues critical for an interaction. Variations on this methodology have been developed to clone genes that encode DNA binding proteins, to identify peptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of interacting proteins to bring a transcription activation domain into close proximity with a DNA binding domain that binds to an upstream activation sequence (UAS) of a reporter gene, and is generally performed in yeast. The assay requires the construction of two hybrid genes encoding (1) a DNA-binding domain that is fused to a first protein and (2) an activation domain fused to a second protein. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter gene; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the reporter gene. The second hybrid protein, which contains the activation domain, cannot by itself activate expression of the reporter gene because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of the first and second proteins tethers the activation domain to the UAS, activating transcription of the reporter gene. For example, when the first protein is a GPCR gene product, or fragment thereof, that is known to interact with another protein or nucleic acid, this assay can be used to detect agents that interfere with the binding interaction. Expression of the reporter gene is monitored as different test agents are added to the system. The presence of an inhibitory agent results in lack of a reporter signal.

[000160] The yeast two-hybrid assay can also be used to identify proteins that bind to the gene product. In an assay to identify proteins that bind to a nGPCR-x receptor, or fragment thereof, a fusion polynucleotide encoding both a nGPCR-x receptor (or fragment) and a UAS binding domain (*i.e.*, a first protein) may be used. In addition, a large number of hybrid genes each encoding a different second protein fused to an activation domain are produced and screened in the assay. Typically, the second protein is encoded by one or more members of a total cDNA or genomic DNA fusion library, with each second protein-coding region being fused to the activation domain. This system is applicable to a wide variety of proteins, and it is not even necessary to know the identity or function of the second binding protein. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions

may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein.

[000161] Other assays may be used to search for agents that bind to the target protein. One such screening method to identify direct binding of test ligands to a target protein is described in U.S. Patent No. 5,585,277, incorporated herein by reference. This method relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two states. When a test ligand binds to the folded form of a target protein (*i.e.*, when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the absence of a ligand. Binding of the ligand to the target protein can be determined by any method that distinguishes between the folded and unfolded states of the target protein. The function of the target protein need not be known in order for this assay to be performed. Virtually any agent can be assessed by this method as a test ligand, including, but not limited to, metals, polypeptides, proteins, lipids, polysaccharides, polynucleotides and small organic molecules.

[000162] Another method for identifying ligands of a target protein is described in Wieboldt *et al.*, Anal. Chem., 69:1683-1691 (1997), incorporated herein by reference. This technique screens combinatorial libraries of 20-30 agents at a time in solution phase for binding to the target protein. Agents that bind to the target protein are separated from other library components by simple membrane washing. The specifically selected molecules that are retained on the filter are subsequently liberated from the target protein and analyzed by HPLC and pneumatically assisted electrospray (ion spray) ionization mass spectroscopy. This procedure selects library components with the greatest affinity for the target protein, and is particularly useful for small molecule libraries.

[000163] Other embodiments of the invention comprise using competitive screening assays in which neutralizing antibodies capable of binding a polypeptide of the invention specifically compete with a test compound for binding to the polypeptide. In this manner, the antibodies can be used to detect the presence of any peptide that shares one or more antigenic determinants with nGPCR-x. Radiolabeled competitive binding studies are described in A.H. Lin *et al.* *Antimicrobial Agents and Chemotherapy*, 1997, vol. 41, no. 10, pp. 2127-2131, the disclosure of which is incorporated herein by reference in its entirety.

#### **Identification of modulating agents**

[000164] The invention also provides methods for identifying a modulator of binding between a nGPCR-x and a nGPCR-x binding partner, comprising the steps of: (a) contacting a nGPCR-x binding partner and a composition comprising a nGPCR-x in the presence and in the absence of

a putative modulator compound; (b) detecting binding between the binding partner and the nGPCR-x; and (c) identifying a putative modulator compound or a modulator compound in view of decreased or increased binding between the binding partner and the nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator. Following steps (a) and (b), compounds identified as modulating binding between nGPCR-x and a nGPCR-x binding partner may be tested in other assays including, but not limited to, *in vivo* models, to confirm or quantitate modulation of binding to nGPCR-x.

[000165] nGPCR-x binding partners that stimulate nGPCR-x activity are useful as agonists in disease states or conditions characterized by insufficient nGPCR-x signaling (*e.g.*, as a result of insufficient activity of a nGPCR-x ligand). nGPCR-x binding partners that block ligand-mediated nGPCR-x signaling are useful as nGPCR-x antagonists to treat disease states or conditions characterized by excessive nGPCR-x signaling. In addition nGPCR-x modulators in general, as well as nGPCR-x polynucleotides and polypeptides, are useful in diagnostic assays for such diseases or conditions.

[000166] In another aspect, the invention provides methods for treating a disease or abnormal condition by administering to a patient in need of such treatment a substance that modulates the activity or expression of a polypeptide having sequences selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257.

[000167] Agents that modulate (*i.e.*, increase, decrease, or block) nGPCR-x activity or expression may be identified by incubating a putative modulator with a cell containing a nGPCR-x polypeptide or polynucleotide and determining the effect of the putative modulator on nGPCR-x activity or expression. The selectivity of a compound that modulates the activity of nGPCR-x can be evaluated by comparing its effects on nGPCR-x to its effect on other GPCR compounds. Following identification of compounds that modulate nGPCR-x activity or expression, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Selective modulators may include, for example, antibodies and other proteins, peptides, or organic molecules that specifically bind to a nGPCR-x polypeptide or a nGPCR-x-encoding nucleic acid. Modulators of nGPCR-x activity will be therapeutically useful in treatment of diseases and physiological conditions in which normal or aberrant nGPCR-x activity is involved. nGPCR-x polynucleotides, polypeptides, and modulators may be used in the treatment of such diseases and conditions as infections, such as viral infections caused by HIV-1 or HIV-2; pain; cancers; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); Parkinson's disease; and psychotic and neurological disorders, including

schizophrenia, migraine, ADHH, major depression, anxiety, mental disorder, manic depression, delirium, dementia, severe mental retardation and dyskinesias, such as Huntington's disease or Tourette's Syndrome, among others. nGPCR-x polynucleotides and polypeptides, as well as nGPCR-x modulators, may also be used in diagnostic assays for such diseases or conditions.

[000168] Methods of the invention to identify modulators include variations on any of the methods described above to identify binding partner compounds, the variations including techniques wherein a binding partner compound has been identified and the binding assay is carried out in the presence and absence of a candidate modulator. A modulator is identified in those instances where binding between the nGPCR-x polypeptide and the binding partner compound changes in the presence of the candidate modulator compared to binding in the absence of the candidate modulator compound. A modulator that increases binding between the nGPCR-x polypeptide and the binding partner compound is described as an enhancer or activator, and a modulator that decreases binding between the nGPCR-x polypeptide and the binding partner compound is described as an inhibitor. Following identification of modulators, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity as modulators.

[000169] The invention also comprehends high-throughput screening (HTS) assays to identify compounds that interact with or inhibit biological activity (*i.e.*, affect enzymatic activity, binding activity, *etc.*) of a nGPCR-x polypeptide. HTS assays permit screening of large numbers of compounds in an efficient manner. Cell-based HTS systems are contemplated to investigate nGPCR-x receptor-ligand interaction. HTS assays are designed to identify "hits" or "lead compounds" having the desired property, from which modifications can be designed to improve the desired property. Chemical modification of the "hit" or "lead compound" is often based on an identifiable structure/activity relationship between the "hit" and the nGPCR-x polypeptide.

[000170] Another aspect of the present invention is directed to methods of identifying compounds which modulate (*i.e.*, increase or decrease) an activity of nGPCR-x comprising contacting nGPCR-x with a compound, and determining whether the compound modifies activity of nGPCR-x. The activity in the presence of the test compared is measured to the activity in the absence of the test compound. Where the activity of the sample containing the test compound is higher than the activity in the sample lacking the test compound, the compound will have increased activity. Similarly, where the activity of the sample containing the test compound is lower than the activity in the sample lacking the test compound, the compound will have inhibited activity. Following the identification of compounds that modulate an activity of

nGPCR-x, such compounds can be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity.

[000171] The present invention is particularly useful for screening compounds by using nGPCR-x in any of a variety of drug screening techniques. The compounds to be screened include (which may include compounds which are suspected to modulate nGPCR-x activity), but are not limited to, extracellular, intracellular, biologic or chemical origin. The nGPCR-x polypeptide employed in such a test may be in any form, preferably, free in solution, attached to a solid support, borne on a cell surface or located intracellularly. One skilled in the art can, for example, measure the formation of complexes between nGPCR-x and the compound being tested. Alternatively, one skilled in the art can examine the diminution in complex formation between nGPCR-x and its substrate caused by the compound being tested.

[000172] The activity of nGPCR-x polypeptides of the invention can be determined by, for example, examining the ability to bind or be activated by chemically synthesized peptide ligands. Alternatively, the activity of nGPCR-x polypeptides can be assayed by examining their ability to bind calcium ions, hormones, chemokines, neuropeptides, neurotransmitters, nucleotides, lipids, odorants, and photons. Alternatively, the activity of the nGPCR-x polypeptides can be determined by examining the activity of effector molecules including, but not limited to, adenylate cyclase, phospholipases and ion channels. Thus, modulators of nGPCR-x polypeptide activity may alter a GPCR receptor function, such as a binding property of a receptor or an activity such as G protein-mediated signal transduction or membrane localization. In various embodiments of the method, the assay may take the form of an ion flux assay, a yeast growth assay, a non-hydrolyzable GTP assay such as a [ $^3\text{S}$ ]-GTP  $\gamma\text{S}$  assay, a cAMP assay, an inositol triphosphate assay, a diacylglycerol assay, an Aequorin assay, a Luciferase assay, a FLIPR assay for intracellular  $\text{Ca}^{2+}$  concentration, a mitogenesis assay, a MAP Kinase activity assay, an arachidonic acid release assay (*e.g.*, using [ $^3\text{H}$ ]-arachidonic acid), and an assay for extracellular acidification rates, as well as other binding or function-based assays of nGPCR-x activity that are generally known in the art. In several of these embodiments, the invention comprehends the inclusion of any of the G proteins known in the art, such as  $\text{G}_{16}$ ,  $\text{G}_{15}$ , or chimeric  $\text{G}_{q5}$ ,  $\text{G}_{q5}$ ,  $\text{G}_{q5}$ ,  $\text{G}_{q25}$ , and the like. nGPCR-x activity can be determined by methodologies that are used to assay for FcR activity, which is well known to those skilled in the art. Biological activities of nGPCR-x receptors according to the invention include, but are not limited to, the binding of a natural or an unnatural ligand, as well as any one of the functional activities of GPCRs known in the art. Non-limiting examples of GPCR activities include transmembrane signaling of various forms, which may involve G protein association and/or the exertion of an influence over G protein binding of various guanylate



nucleotides; another exemplary activity of GPCRs is the binding of accessory proteins or polypeptides that differ from known G proteins.

[000173] The modulators of the invention exhibit a variety of chemical structures, which can be generally grouped into non-peptide mimetics of natural GPCR receptor ligands, peptide and non-peptide allosteric effectors of GPCR receptors, and peptides that may function as activators or inhibitors (competitive, uncompetitive and non-competitive) (e.g., antibody products) of GPCR receptors. The invention does not restrict the sources for suitable modulators, which may be obtained from natural sources such as plant, animal or mineral extracts, or non-natural sources such as small molecule libraries, including the products of combinatorial chemical approaches to library construction, and peptide libraries. Examples of peptide modulators of GPCR receptors exhibit the following primary structures: GLGPRPLRFamide, GNSFLRFamide, GGPQGPLRFamide, GPSGPLRFamide, PDVDHVFLRFamide, and pyro-EDVDHVFLRFamide.

[000174] Other assays can be used to examine enzymatic activity including, but not limited to, photometric, radiometric, HPLC, electrochemical, and the like, which are described in, for example, *Enzyme Assays: A Practical Approach*, eds. R. Eisinger and M. J. Danson, 1992, Oxford University Press, which is incorporated herein by reference in its entirety.

[000175] The use of cDNAs encoding GPCRs in drug discovery programs is well-known; assays capable of testing thousands of unknown compounds per day in high-throughput screens (HTSs) are thoroughly documented. The literature is replete with examples of the use of radiolabeled ligands in HTS binding assays for drug discovery (see Williams, *Medicinal Research Reviews*, 1991, 11, 147-184.; Sweetnam, *et al.*, *J. Natural Products*, 1993, 56, 441-455 for review). Recombinant receptors are preferred for binding assay HTS because they allow for better specificity (higher relative purity), provide the ability to generate large amounts of receptor material, and can be used in a broad variety of formats (see Hodgson, *Bio/Technology*, 1992, 10, 973-980; each of which is incorporated herein by reference in its entirety).

[000176] A variety of heterologous systems is available for functional expression of recombinant receptors that are well known to those skilled in the art. Such systems include bacteria (Strosberg, *et al.*, *Trends in Pharmacological Sciences*, 1992, 13, 95-98), yeast (Pausch, *Trends in Biotechnology*, 1997, 15, 487-494), several kinds of insect cells (Vanden Broeck, *Int. Rev. Cytology*, 1996, 164, 189-268), amphibian cells (Jayawickreme *et al.*, *Current Opinion in Biotechnology*, 1997, 8, 629-634) and several mammalian cell lines (CHO, HEK-293, COS, etc.; see Gerhardt, *et al.*, *Eur. J. Pharmacology*, 1997, 334, 1-23). These examples do not preclude the use of other possible cell expression systems, including cell lines obtained from nematodes (PCT application WO 98/37177).

- [000177] In preferred embodiments of the invention, methods of screening for compounds that modulate nGPCR-x activity comprise contacting test compounds with nGPCR-x and assaying for the presence of a complex between the compound and nGPCR-x. In such assays, the ligand is typically labeled. After suitable incubation, free ligand is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular compound to bind to nGPCR-x.
- [000178] It is well known that activation of heterologous receptors expressed in recombinant systems results in a variety of biological responses, which are mediated by G proteins expressed in the host cells. Occupation of a GPCR by an agonist results in exchange of bound GDP for GTP at a binding site on the  $G_{\alpha}$  subunit; one can use a radioactive, non-hydrolyzable derivative of GTP,  $GTP\gamma[^{35}S]$ , to measure binding of an agonist to the receptor (Sim *et al.*, *Neuroreport*, 1996, 7, 729-733). One can also use this binding to measure the ability of antagonists to bind to the receptor by decreasing binding of  $GTP\gamma[^{35}S]$  in the presence of a known agonist. One could therefore construct a HTS based on  $GTP\gamma[^{35}S]$  binding, though this is not the preferred method.
- [000179] The G proteins required for functional expression of heterologous GPCRs can be native constituents of the host cell or can be introduced through well-known recombinant technology. The G proteins can be intact or chimeric. Often, a nearly universally competent G protein (e.g.,  $G_{\alpha 16}$ ) is used to couple any given receptor to a detectable response pathway. G protein activation results in the stimulation or inhibition of other native proteins, events that can be linked to a measurable response.
- [000180] Examples of such biological responses include, but are not limited to, the following: the ability to survive in the absence of a limiting nutrient in specifically engineered yeast cells (Pausch, *Trends in Biotechnology*, 1997, 15, 487-494); changes in intracellular  $Ca^{2+}$  concentration as measured by fluorescent dyes (Murphy, *et al.*, *Cur. Opinion Drug Disc. Dev.*, 1998, 1, 192-199). Fluorescence changes can also be used to monitor ligand-induced changes in membrane potential or intracellular pH; an automated system suitable for HTS has been described for these purposes (Schroeder, *et al.*, *J. Biomolecular Screening*, 1996, 1, 75-80). Melanophores prepared from *Xenopus laevis* show a ligand-dependent change in pigment organization in response to heterologous GPCR activation; this response is adaptable to HTS formats (Jayawickreme *et al.*, *Cur. Opinion Biotechnology*, 1997, 8, 629-634). Assays are also available for the measurement of common second messengers, including cAMP, phosphoinositides and arachidonic acid, but these are not generally preferred for HTS.
- [000181] Preferred methods of HTS employing these receptors include permanently transfected CHO cells, in which agonists and antagonists can be identified by the ability to specifically alter the binding of  $GTP\gamma[^{35}S]$  in membranes prepared from these cells. In another embodiment of

the invention, permanently transfected CHO cells could be used for the preparation of membranes which contain significant amounts of the recombinant receptor proteins; these membrane preparations would then be used in receptor binding assays, employing the radiolabeled ligand specific for the particular receptor. Alternatively, a functional assay, such as fluorescent monitoring of ligand-induced changes in internal  $\text{Ca}^{2+}$  concentration or membrane potential in permanently transfected CHO cells containing each of these receptors individually or in combination would be preferred for HTS. Equally preferred would be an alternative type of mammalian cell, such as HEK-293 or COS cells, in similar formats. More preferred would be permanently transfected insect cell lines, such as *Drosophila* S2 cells. Even more preferred would be recombinant yeast cells expressing the *Drosophila melanogaster* receptors in HTS formats well known to those skilled in the art (e.g., Pausch, *Trends in Biotechnology*, 1997, 15, 487-494).

[000182] The invention contemplates a multitude of assays to screen and identify inhibitors of ligand binding to nGPCR-x receptors. In one example, the nGPCR-x receptor is immobilized and interaction with a binding partner is assessed in the presence and absence of a candidate modulator such as an inhibitor compound. In another example, interaction between the nGPCR-x receptor and its binding partner is assessed in a solution assay, both in the presence and absence of a candidate inhibitor compound. In either assay, an inhibitor is identified as a compound that decreases binding between the nGPCR-x receptor and its binding partner. Following the identification of compounds which inhibit ligand binding to nGPCR-x receptors, such compounds may be further tested in other assays including, but not limited to, *in vivo* models, in order to confirm or quantitate their activity. Another contemplated assay involves a variation of the dihybrid assay wherein an inhibitor of protein/protein interactions is identified by detection of a positive signal in a transformed or transfected host cell, as described in PCT publication number WO 95/20652, published August 3, 1995.

[000183] Candidate modulators contemplated by the invention include compounds selected from libraries of either potential activators or potential inhibitors. There are a number of different libraries used for the identification of small molecule modulators, including: (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules. Chemical libraries consist of random chemical structures, some of which are analogs of known compounds or analogs of compounds that have been identified as "hits" or "leads" in other drug discovery screens, some of which are derived from natural products, and some of which arise from non-directed synthetic organic chemistry. Natural product libraries are collections of microorganisms, animals, plants, or marine organisms which are used to create mixtures for screening by: (1) fermentation and extraction

of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) thereof. For a review, see Science 282:63-68 (1998). Combinatorial libraries are composed of large numbers of peptides, oligonucleotides, or organic compounds as a mixture. These libraries are relatively easy to prepare by traditional automated synthesis methods, PCR, cloning, or proprietary synthetic methods. Of particular interest are non-peptide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, Curr. Opin. Biotechnol. 8:701-707 (1997). Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to modulate activity.

[000184] Still other candidate inhibitors contemplated by the invention can be designed and include soluble forms of binding partners, as well as such binding partners as chimeric, or fusion, proteins. A "binding partner" as used herein broadly encompasses non-peptide modulators, as well as such peptide modulators as neuropeptides other than natural ligands, antibodies, antibody fragments, and modified compounds comprising antibody domains that are immunospecific for the expression product of the identified nGPCR-x gene.

[000185] The polypeptides of the invention are employed as a research tool for identification, characterization and purification of interacting, regulatory proteins. Appropriate labels are incorporated into the polypeptides of the invention by various methods known in the art and the polypeptides are used to capture interacting molecules. For example, molecules are incubated with the labeled polypeptides, washed to remove unbound polypeptides, and the polypeptide complex is quantified. Data obtained using different concentrations of polypeptide are used to calculate values for the number, affinity, and association of polypeptide with the protein complex.

[000186] Labeled polypeptides are also useful as reagents for the purification of molecules with which the polypeptide interacts including, but not limited to, inhibitors. In one embodiment of affinity purification, a polypeptide is covalently coupled to a chromatography column. Cells and their membranes are extracted, and various cellular subcomponents are passed over the column. Molecules bind to the column by virtue of their affinity to the polypeptide. The polypeptide-complex is recovered from the column, dissociated and the recovered molecule is subjected to protein sequencing. This amino acid sequence is then used to identify the captured molecule or to design degenerate oligonucleotides for cloning the corresponding gene from an appropriate cDNA library.

[000187] Alternatively, compounds may be identified which exhibit similar properties to the ligand for the nGPCR-x of the invention, but which are smaller and exhibit a longer half time than the endogenous ligand in a human or animal body. When an organic compound is designed, a molecule according to the invention is used as a "lead" compound. The design of mimetics to known pharmaceutically active compounds is a well-known approach in the development of pharmaceuticals based on such "lead" compounds. Mimetic design, synthesis and testing are generally used to avoid randomly screening a large number of molecules for a target property. Furthermore, structural data deriving from the analysis of the deduced amino acid sequences encoded by the DNAs of the present invention are useful to design new drugs, more specific and therefore with a higher pharmacological potency.

[000188] Comparison of the protein sequence of the present invention with the sequences present in all the available databases showed a significant homology with the transmembrane portion of G protein coupled receptors. Accordingly, computer modeling can be used to develop a putative tertiary structure of the proteins of the invention based on the available information of the transmembrane domain of other proteins. Thus, novel ligands based on the predicted structure of nGPCR-x can be designed.

[000189] In a particular embodiment, the novel molecules identified by the screening methods according to the invention are low molecular weight organic molecules, in which case a composition or pharmaceutical composition can be prepared thereof for oral intake, such as in tablets. The compositions, or pharmaceutical compositions, comprising the nucleic acid molecules, vectors, polypeptides, antibodies and compounds identified by the screening methods described herein, can be prepared for any route of administration including, but not limited to, oral, intravenous, cutaneous, subcutaneous, nasal, intramuscular or intraperitoneal. The nature of the carrier or other ingredients will depend on the specific route of administration and particular embodiment of the invention to be administered. Examples of techniques and protocols that are useful in this context are, *inter alia*, found in Remington's Pharmaceutical Sciences, 16<sup>th</sup> edition, Osol, A (ed.), 1980, which is incorporated herein by reference in its entirety.

[000190] The dosage of these low molecular weight compounds will depend on the disease state or condition to be treated and other clinical factors such as weight and condition of the human or animal and the route of administration of the compound. For treating human or animals, between approximately 0.5 mg/kg of body weight to 500 mg/kg of body weight of the compound can be administered. Therapy is typically administered at lower dosages and is continued until the desired therapeutic outcome is observed.

- [000191] The present compounds and methods, including nucleic acid molecules, polypeptides, antibodies, compounds identified by the screening methods described herein, have a variety of pharmaceutical applications and may be used, for example, to treat or prevent unregulated cellular growth, such as cancer cell and tumor growth. In a particular embodiment, the present molecules are used in gene therapy. For a review of gene therapy procedures, see *e.g.* Anderson, *Science*, 1992, 256, 808-813, which is incorporated herein by reference in its entirety.
- [000192] The present invention also encompasses a method of agonizing (stimulating) or antagonizing a nGPCR-x natural binding partner associated activity in a mammal comprising administering to said mammal an agonist or antagonist to one of the above disclosed polypeptides in an amount sufficient to effect said agonism or antagonism. One embodiment of the present invention, then, is a method of treating diseases in a mammal with an agonist or antagonist of the protein of the present invention comprises administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize nGPCR-x-associated functions.
- [000193] In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that modulate the function of G protein coupled receptors. Some small organic molecules form a class of compounds that modulate the function of G protein coupled receptors.
- [000194] Exemplary diseases and conditions amenable to treatment based on the present invention include, but are not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Chron's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*e.g.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.

- [000195] Methods of determining the dosages of compounds to be administered to a patient and modes of administering compounds to an organism are disclosed in U.S. Application Serial No. 08/702,282, filed August 23, 1996 and International patent publication number WO 96/22976, published August 1 1996, both of which are incorporated herein by reference in their entirety, including any drawings, figures or tables. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.
- [000196] The proper dosage depends on various factors such as the type of disease being treated, the particular composition being used and the size and physiological condition of the patient. Therapeutically effective doses for the compounds described herein can be estimated initially from cell culture and animal models. For example, a dose can be formulated in animal models to achieve a circulating concentration range that initially takes into account the  $IC_{50}$  as determined in cell culture assays. The animal model data can be used to more accurately determine useful doses in humans.
- [000197] Plasma half-life and biodistribution of the drug and metabolites in the plasma, tumors and major organs can also be determined to facilitate the selection of drugs most appropriate to inhibit a disorder. Such measurements can be carried out. For example, HPLC analysis can be performed on the plasma of animals treated with the drug and the location of radiolabeled compounds can be determined using detection methods such as X-ray, CAT scan and MRI. Compounds that show potent inhibitory activity in the screening assays, but have poor pharmacokinetic characteristics, can be optimized by altering the chemical structure and retesting. In this regard, compounds displaying good pharmacokinetic characteristics can be used as a model.
- [000198] Toxicity studies can also be carried out by measuring the blood cell composition. For example, toxicity studies can be carried out in a suitable animal model as follows: 1) the compound is administered to mice (an untreated control mouse should also be used); 2) blood samples are periodically obtained via the tail vein from one mouse in each treatment group; and 3) the samples are analyzed for red and white blood cell counts, blood cell composition and the percent of lymphocytes versus polymorphonuclear cells. A comparison of results for each dosing regime with the controls indicates if toxicity is present.
- [000199] At the termination of each toxicity study, further studies can be carried out by sacrificing the animals (preferably, in accordance with the American Veterinary Medical Association guidelines Report of the American Veterinary Medical Assoc. Panel on Euthanasia, Journal of American Veterinary Medical Assoc., 202:229-249, 1993). Representative animals from each treatment group can then be examined by gross necropsy for immediate evidence of metastasis, unusual illness or toxicity. Gross abnormalities in tissue are noted and tissues are examined

histologically. Compounds causing a reduction in body weight or blood components are less preferred, as are compounds having an adverse effect on major organs. In general, the greater the adverse effect the less preferred the compound.

[000200] For the treatment of many diseases, the expected daily dose of a hydrophobic pharmaceutical agent is between 1 to 500 mg/day, preferably 1 to 250 mg/day, and most preferably 1 to 50 mg/day. Drugs can be delivered less frequently provided plasma levels of the active moiety are sufficient to maintain therapeutic effectiveness. Plasma levels should reflect the potency of the drug. Generally, the more potent the compound the lower the plasma levels necessary to achieve efficacy.

[000201] As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. nGPCR-x mRNA transcripts may found in many other tissues, including, but not limited to peripheral blood lymphocytes, pancreas, ovary, uterus, testis, salivary gland, kidney, adrenal gland, liver, bone marrow, prostate, fetal liver, colon, muscle, and fetal brain, and may be found in many other tissues. Within the brain, nGPCR-x mRNA transcripts may be found in many tissues, including, but not limited to, frontal lobe, hypothalamus, pons, cerebellum, caudate nucleus, and medulla.

[000202] Sequences selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 will, as detailed above, enable screening the endogenous neurotransmitters/hormones/ligands which activate, agonize, or antagonize nGPCR-x and for compounds with potential utility in treating disorders including, but not limited to, thyroid disorders (*e.g.* thyreotoxicosis, myxoedema); renal failure; inflammatory conditions (*e.g.*, Chron's disease); diseases related to cell differentiation and homeostasis; rheumatoid arthritis; autoimmune disorders; movement disorders; CNS disorders (*e.g.*, pain including schizophrenia, migraine; stroke; psychotic and neurological disorders, including anxiety, mental disorder, manic depression, anxiety, generalized anxiety disorder, post-traumatic-stress disorder, depression, bipolar disorder, delirium, dementia, severe mental retardation; dyskinesias, such as Huntington's disease or Tourette's Syndrome; attention disorders including ADD and ADHD, and degenerative disorders such as Parkinson's, Alzheimer's; movement disorders, including ataxias, supranuclear palsy, *etc.*); infections, such as viral infections caused by HIV-1 or HIV-2; metabolic and cardiovascular diseases and disorders (*e.g.*, type 2 diabetes, impaired glucose tolerance, dyslipidemia, obesity, anorexia, hypotension, hypertension, thrombosis, myocardial infarction, cardiomyopathies, atherosclerosis, *etc.*); proliferative diseases and cancers (*e.g.*, different cancers such as breast, colon, lung, *etc.*, and hyperproliferative disorders such as psoriasis, prostate hyperplasia, *etc.*); hormonal disorders (*eg.*, male/female hormonal replacement, polycystic ovarian syndrome, alopecia, *etc.*); sexual dysfunction, among others.



- [000203] For example, nGPCR-x may be useful in the treatment of respiratory ailments such as asthma, where T cells are implicated by the disease. Contraction of airway smooth muscle is stimulated by thrombin. Cicala *et al* (1999) Br J Pharmacol 126:478-484. Additionally, in bronchiolitis obliterans, it has been noted that activation of thrombin receptors may be deleterious. Hauck *et al.* (1999) Am J Physiol 277:L22-L29. Furthermore, mast cells have also been shown to have thrombin receptors. Cirino *et al* (1996) J Exp Med 183:821-827. nGPCR-x may also be useful in remodeling of airway structures in chronic pulmonary inflammation via stimulation of fibroblast procollagen synthesis. See, e.g., Chambers *et al.* (1998) Biochem J 333:121-127; Trejo *et al.* (1996) J Biol Chem 271:21536-21541.
- [000204] In another example, increased release of sCD40L and expression of CD40L by T cells after activation of thrombin receptors suggests that nGPCR-x may be useful in the treatment of unstable angina due to the role of T cells and inflammation. See Aukrust *et al.* (1999) Circulation 100:614-620.
- [000205] A further example is the treatment of inflammatory diseases, such as psoriasis, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis, and thyroiditis. Due to the tissue expression profile of nGPCR-x, inhibition of thrombin receptors may be beneficial for these diseases. See, e.g., Morris *et al.* (1996) Ann Rheum Dis 55:841-843. In addition to T cells, NK cells and monocytes are also critical cell types which contribute to the pathogenesis of these diseases. See, e.g., Naldini & Carney (1996) Cell Immunol 172:35-42; Hoffman & Cooper (1995) Blood Cells Mol Dis 21:156-167; Colotta *et al.* (1994) Am J Pathol 144:975-985.
- [000206] Expression of nGPCR-x in bone marrow and spleen may suggest that it may play a role in the proliferation of hematopoietic progenitor cells. See DiCuccio *et al.* (1996) Exp Hematol 24:914-918.
- [000207] As another example, nGPCR-x may be useful in the treatment of acute and/or traumatic brain injury. Astrocytes have been demonstrated to express thrombin receptors. Activation of thrombin receptors may be involved in astrogliosis following brain injury. Therefore, inhibition of receptor activity may be beneficial for limiting neuroinflammation. Scar formation mediated by astrocytes may also be limited by inhibiting thrombin receptors. See, e.g., Pindon *et al.* (1998) Eur J Biochem 255:766-774; Ubl & Reiser. (1997) Glia 21:361-369; Grabham & Cunningham (1995) J Neurochem 64:583-591.
- [000208] nGPCR-x receptor activation may mediate neuronal and astrocyte apoptosis and prevention of neurite outgrowth. Inhibition would be beneficial in both chronic and acute brain injury. See, e.g., Donovan *et al.* (1997) J Neurosci 17:5316-5326; Turgeon *et al* (1998) J Neurosci 18:6882-6891; Smith-Swintosky *et al.* (1997) J Neurochem 69:1890-1896; Gill *et al.* (1998) Brain Res 797:321-327; Suidan *et al.* (1996) Semin Thromb Hemost 22:125-133.

[000209] The attached Sequence Listing contains the sequences of the polynucleotides and polypeptides of the invention and is incorporated herein by reference in its entirety.

#### **Methods of Screening Human Subjects**

[000210] Thus in yet another embodiment, the invention provides genetic screening procedures that entail analyzing a person's genome -- in particular their alleles for the nGPCR-x of the invention -- to determine whether the individual possesses a genetic characteristic found in other individuals that are considered to be afflicted with, or at risk for, developing a mental disorder or disease of the brain that is suspected of having a hereditary component. For example, in one embodiment, the invention provides a method for determining a potential for developing a disorder affecting the brain in a human subject comprising the steps of analyzing the coding sequence of one or more nGPCR-x genes from the human subject; and determining development potential for the disorder in said human subject from the analyzing step.

[000211] More particularly, the invention provides a method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of: (a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering the amino acid sequence, expression, or biological activity of at least one seven transmembrane receptor that is expressed in the brain, wherein the seven transmembrane receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or an allelic variant thereof, and wherein the nucleic acid corresponds to the gene encoding the seven transmembrane receptor; and (b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of allele in the nucleic acid correlates with an increased risk of developing the disorder.

[000212] By "human subject" is meant any human being, human embryo, or human fetus. It will be apparent that methods of the present invention will be of particular interest to individuals that have themselves been diagnosed with a disorder affecting the brain or have relatives that have been diagnosed with a disorder affecting the brain.

[000213] By "screening for an increased risk" is meant determination of whether a genetic variation exists in the human subject that correlates with a greater likelihood of developing a disorder affecting the brain than exists for the human population as a whole, or for a relevant racial or ethnic human sub-population to which the individual belongs. Both positive and negative determinations (i.e., determinations that a genetic predisposition marker is present or is absent) are intended to fall within the scope of screening methods of the invention. In preferred embodiments, the presence of a mutation altering the sequence or expression of at least one nGPCR-x seven transmembrane receptor allele in the nucleic acid is correlated with an

increased risk of developing mental disorder, whereas the absence of such a mutation is reported as a negative determination.

[000214] The "assaying" step of the invention may involve any techniques available for analyzing nucleic acid to determine its characteristics, including but not limited to well-known techniques such as single-strand conformation polymorphism analysis (SSCP) [Orita *et al.*, *Proc Natl. Acad. Sci. USA*, 86: 2766-2770 (1989)]; heteroduplex analysis [White *et al.*, *Genomics*, 12: 301-306 (1992)]; denaturing gradient gel electrophoresis analysis [Fischer *et al.*, *Proc. Natl. Acad. Sci. USA*, 80: 1579-1583 (1983); and Riesner *et al.*, *Electrophoresis*, 10: 377-389 (1989)]; DNA sequencing; RNase cleavage [Myers *et al.*, *Science*, 230: 1242-1246 (1985)]; chemical cleavage of mismatch techniques [Rowley *et al.*, *Genomics*, 30: 574-582 (1995); and Roberts *et al.*, *Nucl. Acids Res.*, 25: 3377-3378 (1997)]; restriction fragment length polymorphism analysis; single nucleotide primer extension analysis [Shumaker *et al.*, *Hum. Mutat.*, 7: 346-354 (1996); and Pastinen *et al.*, *Genome Res.*, 7: 606-614 (1997)]; 5' nuclease assays [Pease *et al.*, *Proc. Natl. Acad. Sci. USA*, 91:5022-5026 (1994)]; DNA Microchip analysis [Ramsay, G., *Nature Biotechnology*, 16: 40-48 (1999); and Chee *et al.*, U.S. Patent No. 5,837,832]; and ligase chain reaction [Whiteley *et al.*, U.S. Patent No. 5,521,065]. [See generally, Schafer and Hawkins, *Nature Biotechnology*, 16: 33-39 (1998).] All of the foregoing documents are hereby incorporated by reference in their entirety.

[000215] Thus, in one preferred embodiment involving screening nGPCR-x sequences, for example, the assaying step comprises at least one procedure selected from the group consisting of: (a) determining a nucleotide sequence of at least one codon of at least one nGPCR-x allele of the human subject; (b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; (c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and (d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

[000216] In a highly preferred embodiment, the assaying involves sequencing of nucleic acid to determine nucleotide sequence thereof, using any available sequencing technique. [See, *e.g.*, Sanger *et al.*, *Proc. Natl. Acad. Sci. (USA)*, 74: 5463-5467 (1977) (dideoxy chain termination method); Mirzabekov, *TIBTECH*, 12: 27-32 (1994) (sequencing by hybridization); Drmanac *et al.*, *Nature Biotechnology*, 16: 54-58 (1998); U.S. Patent No. 5,202,231; and *Science*, 260: 1649-1652 (1993) (sequencing by hybridization); Kieleczawa *et al.*, *Science*, 258: 1787-1791 (1992) (sequencing by primer walking); (Douglas *et al.*, *Biotechniques*, 14: 824-828 (1993)

(Direct sequencing of PCR products); and Akane *et al.*, *Biotechniques* 16: 238-241 (1994); Maxam and Gilbert, *Meth. Enzymol.*, 65: 499-560 (1977) (chemical termination sequencing), all incorporated herein by reference.] The analysis may entail sequencing of the entire nGPCR gene genomic DNA sequence, or portions thereof; or sequencing of the entire seven transmembrane receptor coding sequence or portions thereof. In some circumstances, the analysis may involve a determination of whether an individual possesses a particular allelic variant, in which case sequencing of only a small portion of nucleic acid -- enough to determine the sequence of a particular codon characterizing the allelic variant -- is sufficient. This approach is appropriate, for example, when assaying to determine whether one family member inherited the same allelic variant that has been previously characterized for another family member, or, more generally, whether a person's genome contains an allelic variant that has been previously characterized and correlated with a mental disorder having a heritable component.

[000217] In another highly preferred embodiment, the assaying step comprises performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences. In a preferred embodiment, the hybridization involves a determination of whether nucleic acid derived from the human subject will hybridize with one or more oligonucleotides, wherein the oligonucleotides have nucleotide sequences that correspond identically to a portion of the nGPCR-x gene sequence taught herein, or that correspond identically except for one mismatch. The hybridization conditions are selected to differentiate between perfect sequence complementarity and imperfect matches differing by one or more bases. Such hybridization experiments thereby can provide single nucleotide polymorphism sequence information about the nucleic acid from the human subject, by virtue of knowing the sequences of the oligonucleotides used in the experiments.

[000218] Several of the techniques outlined above involve an analysis wherein one performs a polynucleotide migration assay, *e.g.*, on a polyacrylamide electrophoresis gel (or in a capillary electrophoresis system), under denaturing or non-denaturing conditions. Nucleic acid derived from the human subject is subjected to gel electrophoresis, usually adjacent to (or co-loaded with) one or more reference nucleic acids, such as reference GPCR-x encoding sequences having a coding sequence identical to all or a portion of SEQ ID NOS: 1 to 110 (or identical except for one known polymorphism). The nucleic acid from the human subject and the reference sequence(s) are subjected to similar chemical or enzymatic treatments and then electrophoresed under conditions whereby the polynucleotides will show a differential migration pattern, unless they contain identical sequences. [See generally Ausube *et al.* (eds.), *Current Protocols in Molecular Biology*, New York: John Wiley & Sons, Inc. (1987-1999); and

Sambrook *et al.*, (eds.), *Molecular Cloning, A Laboratory Manual*, Cold Spring Harbor, New York: Cold Spring Harbor Laboratory Press (1989), both incorporated herein by reference in their entirety.]

[000219] In the context of assaying, the term "nucleic acid of a human subject" is intended to include nucleic acid obtained directly from the human subject (*e.g.*, DNA or RNA obtained from a biological sample such as a blood, tissue, or other cell or fluid sample); and also nucleic acid derived from nucleic acid obtained directly from the human subject. By way of non-limiting examples, well known procedures exist for creating cDNA that is complementary to RNA derived from a biological sample from a human subject, and for amplifying (*e.g.*, via polymerase chain reaction (PCR)) DNA or RNA derived from a biological sample obtained from a human subject. Any such derived polynucleotide which retains relevant nucleotide sequence information of the human subject's own DNA/RNA is intended to fall within the definition of "nucleic acid of a human subject" for the purposes of the present invention.

[000220] In the context of assaying, the term "mutation" includes addition, deletion, and/or substitution of one or more nucleotides in the GPCR gene sequence (*e.g.*, as compared to the seven transmembrane receptor-encoding sequences set forth of SEQ ID NO:1 to SEQ ID NO:128, and other polymorphisms that occur in introns (where introns exist) and that are identifiable via sequencing, restriction fragment length polymorphism, or other techniques. The various activity examples provided herein permit determination of whether a mutation modulates activity of the relevant receptor in the presence or absence of various test substances.

[000221] In a related embodiment, the invention provides methods of screening a person's genotype with respect to the nGPCR-x of the invention, and correlating such genotypes with diagnoses for disease or with predisposition for disease (for genetic counseling). For example, the invention provides a method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of: (a) providing a biological sample comprising nucleic acid from the patient, the nucleic acid including sequences corresponding to said patient's nGPCR-x alleles; (b) analyzing the nucleic acid for the presence of a mutation or mutations; (c) determining a nGPCR-x genotype from the analyzing step; and (d) correlating the presence of a mutation in an nGPCR-x allele with a hereditary mental disorder genotype. In a preferred embodiment, the biological sample is a cell sample containing human cells that contain genomic DNA of the human subject. The analyzing can be performed analogously to the assaying described in preceding paragraphs. For example, the analyzing comprises sequencing a portion of the nucleic acid (*e.g.*, DNA or RNA), the portion comprising at least one codon of the nGPCR-x alleles.

[000222] Although more time consuming and expensive than methods involving nucleic acid analysis, the invention also may be practiced by assaying one or more proteins of a human subject to determine the presence or absence of an amino acid sequence variation in GPCR protein from the human subject. Such protein analyses may be performed, *e.g.*, by fragmenting GPCR protein via chemical or enzymatic methods and sequencing the resultant peptides; or by Western analyses using an antibody having specificity for a particular allelic variant of the GPCR.

[000223] The invention also provides materials that are useful for performing methods of the invention. For example, the present invention provides oligonucleotides useful as probes in the many analyzing techniques described above. In general, such oligonucleotide probes comprise 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 nucleotides that have a sequence that is identical, or exactly complementary, to a portion of a human GPCR gene sequence taught herein (or allelic variant thereof), or that is identical or exactly complementary except for one nucleotide substitution. In a preferred embodiment, the oligonucleotides have a sequence that corresponds in the foregoing manner to a human GPCR coding sequence taught herein, and in particular, the coding sequences set forth in SEQ ID NO:1 to SEQ ID NO:128. In one variation, an oligonucleotide probe of the invention is purified and isolated. In another variation, the oligonucleotide probe is labeled, *e.g.*, with a radioisotope, chromophore, or fluorophore. In yet another variation, the probe is covalently attached to a solid support. [See generally Ausubel *et al.* and Sambrook *et al.*, *supra*.]

[000224] In a related embodiment, the invention provides kits comprising reagents that are useful for practicing methods of the invention. For example, the invention provides a kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association: (a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x seven transmembrane receptor gene, the oligonucleotide comprising 6-50 nucleotides that have a sequence that is identical or exactly complementary to a portion of a human nGPCR-x gene sequence or nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and (b) a media packaged with the oligonucleotide containing information identifying polymorphisms identifiable with the probe that correlate with mental disorder or a genetic predisposition therefor. Exemplary information-containing media include printed paper package inserts or packaging labels; and magnetic and optical storage media that are readable by computers or machines used by practitioners who perform genetic screening and counseling services. The practitioner uses the information provided in the media to correlate the

results of the analysis with the oligonucleotide with a diagnosis. In a preferred variation, the oligonucleotide is labeled.

[000225] In still another embodiment, the invention provides methods of identifying those allelic variants of GPCRs of the invention that correlate with mental disorders. For example, the invention provides a method of identifying a seven transmembrane allelic variant that correlates with a mental disorder, comprising steps of: (a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny; (b) analyzing the nucleic acid for the presence of a mutation or mutations in at least one seven transmembrane receptor that is expressed in the brain, wherein the at least one seven transmembrane receptor comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 or an allelic variant thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding the at least one seven transmembrane receptor; (c) determining a genotype for the patient for the at least one seven transmembrane receptor from said analyzing step; and (d) identifying an allelic variant that correlates with the mental disorder from the determining step. To expedite this process, it may be desirable to perform linkage studies in the patients (and possibly their families) to correlate chromosomal markers with disease states. The chromosomal localization data provided herein facilitates identifying an involved nGPCR with a chromosomal marker.

[000226] The foregoing method can be performed to correlate the nGPCR-x of the invention to a number of disorders having hereditary components that are causative or that predispose persons to the disorder. For example, in one preferred variation, the disorder is a mental disorder.

[000227] Also contemplated as part of the invention are polynucleotides that comprise the allelic variant sequences identified by such methods, and polypeptides encoded by the allelic variant sequences, and oligonucleotide and oligopeptide fragments thereof that embody the mutations that have been identified. Such materials are useful in *in vitro* cell-free and cell-based assays for identifying lead compounds and therapeutics for treatment of the disorders. For example, the variants are used in activity assays, binding assays, and assays to screen for activity modulators described herein. In one preferred embodiment, the invention provides a purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x receptor allelic variant identified according to the methods described above; and an oligonucleotide that comprises the sequences that differentiate the allelic variant from the nGPCR-x sequences set forth in SEQ ID NO:1 to SEQ ID NO:128. The invention also provides a vector comprising the polynucleotide (preferably an expression vector); and a host cell transformed or transfected with the polynucleotide or vector. The invention also provides an isolated cell line that is expressing the allelic variant nGPCR-x polypeptide; purified cell membranes from such cells; purified

polypeptide; and synthetic peptides that embody the allelic variation amino acid sequence. In one particular embodiment, the invention provides a purified polynucleotide comprising a nucleotide sequence encoding a nGPCR-x seven transmembrane receptor protein of a human that is affected with a mental disorder; wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 under the following hybridization conditions: (a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and (b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and wherein the polynucleotide encodes a nGPCR-x amino acid sequence that differs from a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, by at least one residue.

[000228] An exemplary assay for using the allelic variants is a method for identifying a modulator of nGPCR-x biological activity, comprising the steps of: (a) contacting a cell expressing the allelic variant in the presence and in the absence of a putative modulator compound; (b) measuring nGPCR-x biological activity in the cell; and (c) identifying a putative modulator compound in view of decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator.

[000229] Additional features of the invention will be apparent from the following Examples. Examples 1 and 2 are actual while the remaining Examples are prophetic. Additional features and variations of the invention will be apparent to those skilled in the art from the entirety of this application, including the detailed description, and all such features are intended as aspects of the invention. Likewise, features of the invention described herein can be re-combined into additional embodiments that also are intended as aspects of the invention, irrespective of whether the combination of features is specifically mentioned above as an aspect or embodiment of the invention. Also, only such limitations which are described herein as critical to the invention should be viewed as such; variations of the invention lacking limitations which have not been described herein as critical are intended as aspects of the invention.

## EXAMPLES

### EXAMPLE 1: IDENTIFICATION OF nGPCR-X

#### A. Database search

[000230] The Celera database was searched using known GPCR receptors as query sequences to find patterns suggestive of novel G protein-coupled receptors. Positive hits were further analyzed with the GCG program BLAST to determine which ones were the most likely



candidates to encode G protein-coupled receptors, using the standard (default) alignment produced by BLAST as a guide.

[000231] Briefly, the BLAST algorithm, which stands for Basic Local Alignment Search Tool is suitable for determining sequence similarity (Altschul *et al.*, J. Mol. Biol., 1990, 215, 403-410, which is incorporated herein by reference in its entirety). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first identifying high scoring sequence pair (HSPs) by identifying short words of length  $W$  in the query sequence that either match or satisfy some positive-valued threshold score  $T$  when aligned with a word of the same length in a database sequence.  $T$  is referred to as the neighborhood word score threshold (Altschul *et al.*, *supra*). These initial neighborhood word hits act as seeds for initiating searches to find HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Extension for the word hits in each direction are halted when: 1) the cumulative alignment score falls off by the quantity  $X$  from its maximum achieved value; 2) the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or 3) the end of either sequence is reached. The Blast algorithm parameters  $W$ ,  $T$  and  $X$  determine the sensitivity and speed of the alignment. The Blast program uses as defaults a word length ( $W$ ) of 11, the BLOSUM62 scoring matrix (see Henikoff *et al.*, Proc. Natl. Acad. Sci. USA, 1992, 89, 10915-10919, which is incorporated herein by reference in its entirety) alignments ( $B$ ) of 50, expectation ( $E$ ) of 10,  $M=5$ ,  $N=4$ , and a comparison of both strands.

[000232] The BLAST algorithm (Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 1993, 90, 5873-5787, which is incorporated herein by reference in its entirety) and Gapped BLAST perform a statistical analysis of the similarity between two sequences. One measure of similarity provided by the BLAST algorithm is the smallest sum probability ( $P(N)$ ), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a GPCR gene or cDNA if the smallest sum probability in comparison of the test nucleic acid to a GPCR nucleic acid is less than about 1, preferably less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

[000233] Homology searches are performed with the program BLAST version 2.08. A collection of 340 query amino acid sequences derived from GPCRs was used to search the genomic DNA sequence using TBLASTN and alignments with an E-value lower than 0.01 were collected from each BLAST search. The amino acid sequences have been edited to remove regions in the sequence that produce non-significant alignments with proteins that are not related to GPCRs.

- [000234] Multiple query sequences may have a significant alignment to the same genomic region, although each alignment may not cover exactly the same DNA region. A procedure is used to determine the region of maximum common overlap between the alignments from several query sequences. This region is called the consensus DNA region. The procedure for determining this consensus involves the automatic parsing of the BLAST output files using the program MSPcrunch to produce a tabular report. From this tabular report the start and end of each alignment in the genomic DNA is extracted. This information is used by a PERL script to derive the maximum common overlap. These regions are reported in the form of a unique sequence identifier, a start and the end position in the sequence. The sequences defined by these regions were extracted from the original genomic sequence file using the program fetchdb.
- [000235] The consensus regions are assembled into a non-redundant set by using the program phrap. After assembly with phrap a set of contigs and singletons were defined as candidate DNA regions coding for nGPCRs. These sequences were then submitted for further sequence analysis.
- [000236] Further sequence analysis involves the removal of sequences previously isolated and removal of sequences that are related to olfactory GPCR's.
- [000237] nGPCR-x cDNAs were sequenced directly using an ABI377 fluorescence-based sequencer (Perkin-Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISM<sup>TM</sup> Ready Dye-Deoxy Terminator kit with Taq FS<sup>TM</sup> polymerase. Each ABI cycle sequencing reaction contained about 0.5 µg of plasmid DNA. Cycle-sequencing was performed using an initial denaturation at 98°C for 1 minute, followed by 50 cycles using the following parameters: 98°C for 30 seconds, annealing at 50°C for 30 seconds, and extension at 60°C for 4 minutes. Temperature cycles and times were controlled by a Perkin-Elmer 9600 thermocycler. Extension products were purified using Centriflex<sup>TM</sup> gel filtration cartridges (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product was loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B tabletop centrifuge) at 1500 x g for 4 minutes at room temperature. Column-purified samples were dried under vacuum for about 40 minutes and then dissolved in 5µl of a DNA loading solution (83% deionized formamide, 8.3mM EDTA, and 1.6 mg/ml Blue Dextran). The samples were then heated to 90°C for three minutes and loaded into the gel sample wells for sequence analysis using the ABI377 sequencer. Sequence analysis was performed by importing ABI377 files into the Sequencer program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp were obtained. Potential sequencing errors were minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers annealing at different locations until all sequencing ambiguities were removed.

[000238] The following Table 5 contains the sequences of the polynucleotides and polypeptides of the invention. The transmembrane domains within the polypeptide sequence are identified by underlining.

Table 5

The following DNA sequence Seq-2227 <SEQ ID NO. 1> was identified in *H. sapiens*:

AATGTGGAAGTCATCAGCATCAAGGTATTTGAGACCATGAGACCAGGGGAGGTCACTAAGGGACTGAGTGT  
GGAAAGAAAAGAAAAGTTCCAGGACTGACCCCTGAGCCGTCCAGGGTCAGGAGTCAAAATCATGAAAAGC  
AATGAAAAGAAATGAAGCCAAGAGCAGCCAGTGCATGAGAAGAAAAGTGAAGTGGTGCCCTGGAAGCCAGG  
GAAGAACATGTTTCCAGGAAGGAGGGAGTGAACAGGAGGATGCCGCTGACACATCGGGTACCGTGAAGACA  
GAACTGAACTGAGCAGGCTGGTTAGCTAGTGGAGGGCATTAGTGAGCTGGGAAGCTGGTCAGTTGAGTCGG  
GGTAAAAGCTGATGGCAGGAGGTTCCAGAGGGAATGGGAGAAGATAAATCGGAAGAATGGCTATAGCCCGC  
TGAAGCGAAGGAGAGAGGTAGAAGTGGGAGTGGGAGAGGAAAGAGGAACAAGAGGTTTCTGGTTTGTAT  
GTAAGATGGAGGAAATGTGCTTATGAATAAGCTAAAAAATGCTGGTGGCTGATGGATAATGTCTAATAGG  
GAGG

The following amino acid sequence <SEQ ID NO. 129> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 1:

LPIRHYPATSIFLAYS AHFLHLTQNQKPLVPLSSPTPTSTSLLPFSGLPFFRFIFSHSLWNLLPSAFTPT  
QLTSFPAHCPPLANQPAQFSSVFTVPDVSAASSCSLPPSWKHVWLPGHHSVFFSSHLLLASFLIAFHDF  
DSPWTAQGSVLELFLFFPHSVPPPLVSWSQIPCLPH

The following DNA sequence Seq-2228 SEQ ID NO. 2> was identified in *H. sapiens*:

TTGAATTCAGAATGTTATAATTTGTGCTACAATCAGTTGTCTAAAAGCTATGTTTATACCTATGCCTATTT  
CTTTTGTGACTTAAATCTTGGAGGCCAGCCATATTTAGTTATTTTGTAAAAGTTACCAAATTACAATATT  
AGGCACATTTTCAAATGATGCTCTCGTCTTCTATTATGCTTGGGTCGTTTATAATATATTGAGGTTTT  
GCAAAAACAACTGATGTAAGATACAGTATGCATTATCTTACATCATACATACATACATATATATGA  
AAAGGAGAGAGAGAGAGAGACAGTAATAGAGATCTATGAAATTGGAATCAGGTTAAACATATTTCAA  
CTGACCCCTAAATTCCTTAAAAATATTTCTTTGTAGGTATTCTGATTTAAACCACTAGTTTAAATGAAATGCA  
ACCCTAATTAGGGTTACTCTGTGTTATTCTTACAGTGATTCTTCTTAAGTCCAACTCCTCAAGAT  
ATTTGTGTCTATGTATTTTTCTCTGTAAGAGACAATTTTGGGTATTCTTAATTAAAGCAGCCACTGT  
CACAGTAAGATAAACTATCAGAATGTTGGGGAGGGAGGA

The following amino acid sequence <SEQ ID NO. 130> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 2:

LNSECYNLCYNQLSKSYVYTYAYFFCDLNLGGQPYLVIFVKVTKLQYAHFSKCSRLIMLGFSFIIYGFAKT  
NCKIQYALSYIIHTYIHIYEKERERERQRYLWNQVKHISTDPKFLKNISLVFFKPLVNATTNGYSVLFLQ  
FILLSSKLLKIFVCLCIFSLETILGILNKQPLSQETLSECWGR

The following DNA sequence Seq-2229 <SEQ ID NO. 3> was identified in *H. sapiens*:

CTTTGGTGGTCTCTTACACGGATGCATGAAACACACCTCATGTAAATTGAAAATAAACAACTCGGACTAC  
CCTCTTTGGGTCCCTCCCTTTCTATGGGAGCTCTGTTTCACTCTATTAAATCTTGCAACTGTACTCTTC  
TGGTCTGTGTTTGTATGGCTGGAGCTGAGTTTTCGCTCGCTGTCCACCACTGCTGTTTGTGCTGCCATCGCA  
GACCCGCTGCTGACTTCCATCCCTCTCAATCCGGCAGAGTGTCGCTGTGCTCCTGATCCAGCAAGTTGCC  
CATTGCCGTTCTGATCGGGCTAAAGGCTTGCCATTGTTCTGTCACGGCTAAGCGCCCGGGTGCCTCCTAA  
TCGAGCTCAATACTAGTCACTGGGTTCTGTGGGTCTCTTCCGTGACCCACGGCTTCTAATAGAGCTCTAA  
CACTCACCACATGGCTCAAG

The following amino acid sequence <SEQ ID NO. 131> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 3:

FGGLLHGCMKHTSCKLKINKLGLPSLGLPLPYGSSVFTLLNLATVLFWSVFMAGAEFSLAVHHCCLLP  
SRCLPSLSIRQSVRCAPDPASCPLPFLIGLKACHCSCTAKRPGASSSSILVTGFCGFSSVTHGFSNTHHM

AQ

The following DNA sequence Seq-2280 <SEQ ID NO. 4> was identified in *H. sapiens*:

TCTGCAAATTTAAGATTATTCCAGTATAAAAAATTGTCAAAAACACTAATAATAAGAAGGCCCAAAAGGTG  
AAACAGATATTGGCAAAGCTCTTGTGGTATGAGTAGAGGTACAGGGCCTGAGTCCTGACTGCTCAGCCTCT  
TCTCACTCCTCACTCCCTCCAGGCTGGCTCCCTCCTTCCCCAGGTCCCCAGGGTTCTCTGTACATATTC  
TGAAAAGTACTGCCCTGCAGAACTAAATGCAAGCTCCTCAACATATCTTCTGGGGCCCTTCATATTCTTAC  
CCTTGGCTAGCTTTTCATCTTCATCATCTGGTGACCTCTTGCTGCTATATGTATTTCTGTATTTATTACCT  
TCATATATTTTGAAGGCACCTTTTTTCTCAAGCAGATCCTGACCTTCTTGTGATTTTGAACATGCTACT  
TTTTTCAGCTTGGAAGACCATTTCTCAAGCTTACTCACCTCAAAAACCTTTCAAAAATCATCTTAGAATTC  
AGCTTAAGAGTGAGCCTTCTCTTGAAGACTCTAAGGGAAAGGGACACCTTCTGAAATGTTTCTACAATA  
GCA

The following amino acid sequence <SEQ ID NO. 132> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 4:

LQIDYSSIKNCQKHEGPKGETDIGKALVVVEVQGLSPDCSASSHSSLPSRLAPSFPRSPGFSVTYSEKYCP  
AELNASSSTYLLGPFIFLPLASFHLHLVTSCLLYVFLYLLPSYILKALFFLKQILTFLILNMLLFSAWK  
TILKLTHPQKLFKNHLRIQLKSEPSLERLGKTPFNVSTIA

The following DNA sequence Seq-2281 <SEQ ID NO. 5> was identified in *H. sapiens*:

CGTTTTCTACTATGGTGCTGATTAGTTTTTTGGTAAGATTCTTGATCACAGAAGATATCAAATACACAGA  
CTGAAGTTCAACACTTATTTTGAAGCTAGAAAATAAAAATATATATACATTCTTGGAATAATCTATTGCAT  
ACATACAGGGTGAAAAAATGAAGTAACTTCATAAACAGTATCCATTTGTAAAATTCCTAGAGAATTCC  
AGGGTATTTCCATGGAACTATGCATTGTCAAGTTTTTAATTAGTCACACTAATTTCCCCTTTGGTGTTAA  
CTATCAAAGCATACTCAAATCTTCTCATTGGCATTACACATTGGAGGTGCTCAATAAATGTATGTTGGAC  
TTCAGTGTGGTGTTCTGCTAAGTACTTAAATTCAT

The following amino acid sequence <SEQ ID NO. 133> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 5:

IEFVLSRTPHSPTYIYAPPMCNANEEDLSMLLPKGEISVTNKLDFHGNLTLEFSSEFYKWILFYEVTSF  
FSPCMYAIIDYSKNVYIFLSSFKISVELQSVYLISSEVIKNLTKKLITIVGK

The following DNA sequence Seq-2282 <SEQ ID NO. 6> was identified in *H. sapiens*:

AGGGCCCTCATCCCACTTGATGATTATGGTTTTCTTTGCTCAGAGGAACTAAGGTCTAGCTCCCTGCTAA  
CGCAGCCTTTGGGAAGCCAACTTTACCCGAGAACCTGGAATCCGGCCCCTCTCAGAGGCCCGGAAG  
GCAGTGGGGCTTGGCAGGGCTACCCGTTCTGAATTCATGTGCACCGGACTGGGTCCCCTGGAGCTACGCC

The following amino acid sequence <SEQ ID NO. 134> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 6:

GPHTLWFSLLRGNGLAPCRSLWEANTFTREPWNPAPLRGPGRQWGLAGLPVLNSCAPDWVPWSYA

The following DNA sequence Seq-2283 <SEQ ID NO. 7> was identified in *H. sapiens*:

AAACAGCATTTTCATGAAAAATGTTCTCACCTCGTTGTGCTAGTTCGTGGTATCTTTTTCTTCCAGGCTT  
ATTCTTCCCAAATGACTACAGTTTTTGTGGCATTCTCTGAAGGTATACTTGAGATCTCTTTAAGAGTC  
AGAAAAGCTACCTGAAATTCAGGCAGCTTCCTGTTGGGCTCACGTTTTGCAGAATCCACGCTTGGTGTGC  
AGAAGGTGGGCAAGGTGTTTGAACAAACAGGAAGCACCTGTGAATGTGTGAATTTATTTCTGGAAGCAGAA  
GGCTCCCTCTGAGATGGCTCTAGATGCTTCCTGCTGTTCCACCTATGAGCATTTTGCAAGGCCTTTCAGTA  
CTTTGGGGCTATGAACAGGCTTCCGAATGGCAGGATTATTGGAAAATCTGGGA

The following amino acid sequence <SEQ ID NO. 135> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 7:

NSIFMKNVLTLLVVLVRGIFFQAYSFPNDYSFCWHFSEGILEISLRVRKATNCRQLPVGLTFCRIHAWCAE

GGQGVKNRKHLMCEFISGSRRLPLRWLMLPAVPPMSILQGLSVLWGYEQASEWQDYLENLG

The following DNA sequence Seq-2284 <SEQ ID NO. 8> was identified in *H. sapiens*:

TTAAAAACAAGTGGTAATTAAATTTAGCTGGCAAGCTAAAGTTTGTCAATTCTTGGTCTAGAAGAAGAAAC  
AGACACAAGCCAAAAAATTATGCATATGATAACACGTGCAAAGATCCGGTGGCGAGAAGACATATCAAGCT  
TTGGAGGCACTGATAGGAGACCAATGGAGCTGCTTCACGGAGAGACACATGAGTGAGGCTGGAAAGGGAGG  
AAGGGGCAGGCCAGCAGGGTCTTGTAGGACACTTAGGAGTTTGGTCTTTACAATATTGACAGTTGGCAATT  
TTTGATTATTTTAAAGCAGGATGAAGACATGATCAGATTTGAGTTTCAAAAGCTCACTCACTGCAGTGTTA  
GAATGAGTTGGGTTAAATTTTCTCATCTGAAACATAAGGATGGATACACTTGCCCTGTGTATTGAACAGGT  
CATTGTGTAATCAGTGATCACACAAGATTTATACAAGGTGCATAGAAGTGTATTTATGAAATATAAATGCTA  
TAGAAAATTACACAGCAATATTTTACAGGAAGCAATACCACCAGATGGTCATATTCTTTCAAGTTTTTCT  
GTGAACAAAGGCAGTCTGAACATCAAAAAT

The following amino acid sequence <SEQ ID NO. 136> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 8:

ILVQTAFVHRKNLKEYDHLVLLPVKYCCVIFYSIYISNTSMHLVILCDHLHNDLFNTQGKCIHPYVSDEK  
IPNSFHCSEAFETQISCLHPANNQKIANCQYCKDQTPKCPTRPCWPAPSSLSSLTHVSLREAAPLVSYQCL  
QSLICLLATGSLHVLSYAFFGLCLFLLLDQELTNFSLPAKFNYHLFL

The following DNA sequence Seq-2285 <SEQ ID NO. 9> was identified in *H. sapiens*:

CTAAACTCTCTGTAGAGAGCATGCAGTGACAGTTTAGCCTATGCTACCTGAAGTGGAATAGATCATTCTT  
TAAATAAATCACTTGTGCTGACTTGGTAACTCAAGGAGACCACACTTATTATTTCTCTCAATTCGCAACT  
ATCTTTGGAAACAAGACGATTTTATTTCTTGCTTAGCCTTACCTCTTCTATTACAGAAAATCAGCAGCAC  
GCTAATGATGTCTTAAAAGTACAAAGTCACTTGTAAAGGACATTAGGATCCCTGGCTAGGTAAGAACTCT  
GTATGACACAGTTTTTCAAGTGACACCTATTCAAATTTGCAAGTGATATCTCTTTTGTACTGATTTAGCCT  
GTACCTGAAAGCAATAGCCATACACATGAGTATACTGAATTAAGTGCCTAGTAGATGACTTTCTATAAGA  
AAGAGGGGGAAACACCCAAATTACATTCAAAGACATTACTGGAAATTAATTATGTATAATTTCCAGTATAA  
TGCAAAACATTTATCCTCGCGTTATCCAGTTTCTAAGTGTAGGAGAAATTGCATTTATTTCTTAAATTTAA  
CACTACTACGCTTAAACAAAAAGTCATGCTAGTATGCATATTTCCACAAATCTTATAAAATAGATGATAT  
TTTCA

The following amino acid sequence <SEQ ID NO. 137> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 9:

LNSLRACSDSLAYATSGNRSFFKITCADLVTQGDHTYYFLSIRNYLWKQDDFISCLALPLLFTENQQHAND  
VLKVQSHLRTLGLSLARETLYDVFVKCTPIQNCKYLFCTDLACTKQPYTVYIKCTSRLSIRKRGKHPNYIQR  
HYWKLIMYNSQYNANIYPRVIQFLTVEIAFIPNLTLRLKQKVMLVCIFPQILN RYF

The following DNA sequence Seq-2286 <SEQ ID NO. 10> was identified in *H. sapiens*:

CTGGAAGGAAAAATCTGACTATTTCTCCACTACAGCCATTTTCTAAAAGCTTCTGGAGGCTGTGTGCATC  
CCTTCTAGTGAAGTATCTGGGAGTTCACCCCTGTGTTGCAGAGAGAAGACTCCACCCCTCCTCCCTCCCCAA  
AGCTACCACAGCTTACTTGAGAATAACAACAATATCATGTGACCCTTACATAGCAATGGTCAATTTATCCA  
TTGATCTCTACTATATAATGGGATTGTGACAGCAATTTTGTAAAGTTGGATGAGGATTAATTTTATAAATGA  
GAATACTGGAGGCTCGGAGAGGTCACCTGTGATGGTCACATACCTGGCTCCATGTACACTATTTCCCTCCT  
GGGCCTTTGCCATACTGTGCTGAGCTGCAGTTGGGGAAATATCTCAGGGACGTGCCTCATCAGGGTAGTCT  
GTTGTGGACAGCAGAGAGATGGGTGCGTCTCTGGCCACTTATAGCCACACACAAGTGCCACTCAGAACA  
CTGGCCCTGACCCCTAAAGAATCAATTAGTGGTCTGCCTGCAGCGAAACTGTTTCAAGGCCCTTTTAGTGCT  
TCTCACATTTCCACCAGGTATCCCCCTTGGCCCCATGAGCTTGACAGTCTTCCAAAATATTTCTGACAACCC  
CAGTGAGTGATGTTTACCAGATGCTGATC

The following amino acid sequence <SEQ ID NO. 138> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 10:

GKEKSDYFSTTAIFKLEAVCIPSSSEVSGSSPCVAERRLHPSSLPKATTAYLRITTISCDPYIAMVNLSID  
LYYIMGLQQFCKLDEDFYKEYWRLGEVTCDGHI PGSMYITISLLGLCHTVLSCSWGNI SGTCILIRVCCGQQ  
RDGCVSGHLPHTQVPLRTLALTLKNQLVVLQNRNCFQGPFSALTFHQVSPLAPAQSSKIFLTPVSDVHQM  
LI

The following DNA sequence Seq-2469 <SEQ ID NO. 11> was identified in *H. sapiens*:

GGGGTTGGAAAGATCACTCTGACACTGTGGCGGGGGCCTGCTGGGAGCAGGAGTGGAAAGCAGGGATGGGAC  
TTTTCTCTGCAGCCTACCTAGATCATGGTACTCACAAGCCTTGTTCTCGCAGGCCTCACCTGCTTTTCAGC  
CCGGGGCGCCCTGGGCAACCAGAGTGCAGAGGACACGTGTTTCATCAGTCTTCACCCCGTACTGGCAACTTT  
CTTGGTGCAATGCCCTTGACTGGGCACTGGGAAGGCTGTAAAATCAGTCTTCACCCCGTACTGGGAACCTTT  
CTTGGTGCAATGCCCTTGACTGGGCACTGGGAAGGCTGTAAAACAGTTTCTGCCCCCAAGAGGAGCAAAG  
GGTGGGCTTGACCCAGATAACTGCCCCACAAATGGCATGTGCTGAAGACCTGGGGGCGCAGGTGCTGTGG  
CCCTCATGCTTTTCCCGTGCTCCTGGAAGGAGGCTCAATGCCTTGGCGCCAGCTTCATGGTTCTTGGGGC  
TCCTG

The following amino acid sequence <SEQ ID NO. 139> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 11:

GWKDHSDTVAGACWEQEWKQGWDFSLQPTIMVLTSVLVLAGLTCFSARGALGNQSAEDTCSVFTPYWQLSW  
CNALDWALGRNLNQSSPRTGNFLGAMPLTGHWEGCKNSFCQEERVLHPDNCPTNGMCRPGGAGAVLML  
FPVLLEGGSMPPWRQLHGSWGS

The following DNA sequence Seq-2470 SEQ ID NO. 12> was identified in *H. sapiens*:

CAATAATGATCTAGGACAGAGATGTTCAACCCCTTTGGGGATCTCAGGGCCAGCCAGGGGAGCAGGGGTGA  
GTGTCGGAAGTCTTGCTGTCCACAGCCATCCTCAACTCCCCAAACCTGCAACCAGGGCCGCTCAGCTTTCA  
TGAGCTTACCTCCCAGCCTCTTTTGTAGTGTGCTTTGGAGAAAGAATGACGTGGTCAAAACCTTTGAAA  
ATCAGGATTTAAACAATAAATTTTAAATATAAGCAAGATGCTTTCCTATAGGAAAAAAGAATACATGAAC  
GAAATTCAGCTTTCTACATCTGCAAATCAACTGATAGTGAATTTAAAGGGCCATTTCTGCCCCTGTAATG  
ATCACTGATGACATTGACAGGCTGCTTCTCTCTTTCTTGGCTGCACCTCATGGGGGCATCCTGGGACCTGC  
TTTGTGGTCAGGGTGTAGAGAAGACCCCCCAGCTGTCAACTCTTTAACTGTCAACATCTGCGTCAACATC  
TGCTTAGAGGATCTTAGTCACACACCAACAATTCTTACTTAAATATAAAGGGCCACGGGGATGAGTCTTT  
GAACTCTGCGCCCTCCCTTCCCTTGCAAGGCCAATGTGTA

The following amino acid sequence <SEQ ID NO. 140> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 12:

IMIDRDVQPFGLDRAQPGEQGVSEVLLSTAILNSPNLQPGPLSFHELTSQPLFCCLWLRKNDVVKTFENQDL  
NNKFIARCFPIGKKEYMNEIQLSTSANSTDSEFKGFPFALSMLTLTGCFSLSWLHLMGASWHLLCGQGVKE  
TPPAVNSLTVNICVNICLEDLSHTPTILTNIKGHGDSELSNAPSLSLQGMQMC

The following DNA sequence Seq-2471 <SEQ ID NO. 13> was identified in *H. sapiens*:

TACCCTCCCTTCTGCCCTCCTAACGAGAACTGTGAGTTGGATGCAGAAGTTTCTAAAAAATAATGAG  
TATTGAAATTGGCTGTGTCATCAGTGAAGAAAAGCAACATCCCTACCACCCCTCAAAGAGACATTAAAGT  
AGTTGGATTAAGGGCAGGGAGTATTTGCTTTCCGATTAGTGATAATGTGAGTGCTTAATGAAATGACTA  
ACACATTCCCTGATTATAGAGCTGGTCAGTGGATCTTGCTGAGTTTCTGTGGACCTATGTGAAATGATCG  
GCATCTGTTTCAGGGTTTACTAGGTGCTAAGCACCTTTACATGTGACATCCATTGAATGCTCACAACACCCC  
CAGGAAATTGGTACCAGTGTTATCCTCATGGTACAGTGAAGGATACTGAGACTTAGGTTGCATAGCCTGCA  
GGTTGGACACACTTCTTCTGACTGCTGGGGAGCTGTGCTTTTAACCACTGCTGATCCGGCTTGTTTTCCC  
CAGATGCAGGCCCTGGGGTAGTCTCCTTTCTGGACTGAGAAGAGAAGAATGGAGAAGCCCTCTTCCCATTG  
TGAGTAGACAGTAAATGGTTAGAGAGTAGCCAGGAGCTTCTGGAACCAGAGTTCCTTTCTCAGCTGAAA  
AGAACCCTAAGAGTAGACTGCCTGGGATGGCGTGCGGGATGGGAGGATCACTGGACCTGTGGGCCAGAAAC  
TTGGGTTTGAGTCCCAGCTCTAGCTTTGCTTAGTTGTGTGACTCTCAGAAAGTCATCCAACCTCTGTGGT  
GCTTATTTTTCAGTGATAGTACCTGTGGGCACATAGGACCTGTGGGGAATGATTACCTTTTAGCCCCATCCT  
ATGACAATATGGTTTGTGTTTAAATCCAGGTTAGCACTGACTTCTCACTGACTTCTTGTGTTTTTCAGAG  
TGCCTTTCATTGGTTTGGCTTTGGCTACACAGCACTGGTTGTTTCTGGTGGGATCGTTGGCTATGTAAAA  
ACAGGTA

The following amino acid sequence <SEQ ID NO. 141> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 13:

YLFLHSQRSHQKQPVLCSQSQTNAKALKHKRSQEVSANLDLKTNHIVIGWKVIIPHSYVPTGTITENKH  
HRGWMTFESHNAKLELGLKPKFLAHRSSDPPIPHAIPGSLLLGFFSAEERNSGFQKLLATLPFTVYSQWEE

GLLHSSLLSPERRLPQACIWGKQAGSAVVKSTAPQQSERSVSNLQAMQPKSQYPSLYHEDNTGTNFLGVLA  
FNGCHMRCLAPSKPTDADHFTVHRKLSKIHPALSGNVLVISLSTHIITKSESKYSRALNPPTLMSLLRGGR  
DVAFLHCNSQFQYSIFFFRNFCIQLTVLVRRAELEG

The following DNA sequence Seq-2472 <SEQ ID NO. 14> was identified in  
*H. sapiens*:

ATTAGGAGATTTATTTTAAGGAATTGGCTCACATGAATGTGGGGGCTGGCTAAGCAATCTGAAATCTGTGA  
AGCTGAAACTCAACAGGTATGGGCCAAAGCTTTTATCCACAGACAGACTATCTTTTCTTTTGGGACAAGC  
TTCAGCCCTGCTTTTGTAGTCTTCCCACTGATTGAATCAGTCCTACCCATAATATACAAACATAAATCCTG  
AATTTTTTTTACACTTACCAAAATCAACTGGTGTGGACTGAATTACATCTGCAAAAGGTCATCACAGAAA  
CAGCTGGATTATCATTTTGATTGAGTAACCTGGGGGCTATAGCCTAGCCAAGTTAACATATCAAAGTCACTGC  
AGATGGGTGAGTTGAATAAAATCTTTACCAAAGATGATGCTTAGAATGCATTCCAACAAAAGTTTTAATAT  
TTAATGACAGAAAAGGAAATATTATACATACCTAAAAGCTTCTCCTACTGTATTAACTCTCCACCAA  
GGATTTTCTGAAGGAAACACTTGAAGGTATTGATGACAACCTGTATAAATAAAGAGTTATTCTGATTATTA  
TTGAGAGATATAATGCTCATTTTATTTATTACATTTGGAGAGCTCTAAATAAGTTTGTAAATTATGGCCTGT  
AAAAGAAAAAGTGTAAATTTCTTTTAAATGGACAACCTAAGATTTTTTTTATAATATTGAACTCATTAGGC  
CAAAACATGCATTCATTTTGGGATTATTTAAATGAATTAATTCATTCAACAGATATATAATTGAAACATAG  
TATACAGAAGACATTGTGCTAGATTCTGGCGATAAAATGGTGAATAAAACCAAGACTGCCCTCCCTTCAA  
GAATTTTATGATTAGTCATGGAAAAAATACATTAATCAAAATATTGACACGAAAAAATTATCACAAACTGC  
GATAATTCGTGATTATAGTTGCAATGAGTCTATGTTCAATGATTCTTGATTTTTTCTGTGTGTTAGAAA  
GCTTAC

The following amino acid sequence <SEQ ID NO. 142> is the predicted  
amino acid sequence derived from the DNA sequence of SEQ ID NO. 14:

KLSNTQKKSRIIEHRLIATILSRIIAVCDNFFVSIFDCIFSMTKSNSREGQSWFYSPFYRQNLAQCLLYTM  
FQLYICMNFIIIPKMHVLAVQYYKKILVHLKGNHFFLLQAIITNLFRALQMIKALYLSIIIRITLLFIQL  
SSIPSSVSFRKSFGEENTVGRKLLGMYNISFSVIKYNFCWNAFASSLVKILFNSPICSDFDMLTWLGYSP  
QLLNQMIQLFLPFADVIQSTTSIWVKKFRIYVCILWVGLIQSVGRLLKQGSLSQKEKIVCLWIKALAHTC  
VSASQISDCLASPHIHVSQFLKINLL

The following DNA sequence Seq-2473 <SEQ ID NO. 15> was identified in  
*H. sapiens*:

CTCTTTGAGGCATATAATGCTCATTCCATTTTCTACTGCTTAACCTCTCTTTTATATTTTCTATAACTC  
TCTTTCTTCACTTTCCAGAGTTCACTAATTCATTCTTTGGCTGGGTTTAATCTAGCTTTACCTTATTCAC  
GAGTTTTTTTAAATAAATATTTGAATTTCTATGTGACATTTAAACATTTCTATGTAATTTGCTGTAACATA  
CTTGACATACTGAAATTTTACTTAAAGTGTTATCTTGCTACATCCTCAAATGAGTATCAGTATGTTCACTC  
TTTTTCTCTAGAGATAACTGTTTCTTTTGAACCTTCTACATTTCTTTTTTCTATGTTTTCAATTTTTCCA  
ACTCTATTACAAAAATTTAGACAGAAAAATCTGAACAAATGGTACAATTAACATCGAAATTTTCTTAGAT  
TCTAAGATTATCTTTTCTGATTGCTTTTCTCTTTCTCTGATGTTGATTTCATCACACCATTTGAAGTT  
AAGTTTCCAAGTAACTGACAGAGATAGAAATGAATAGTGTTATTTTTAGTGAATTGGGAGGGGCACAGG  
AGAACCCTCTAAAGCATCAGGAAATGTCCTACATCTTAATCTACATGGTAGTTACACATGTAAAACTCTG  
AGCGATATACTTCAAGTTTGTACCTCTACTGTGTATAAGTCCATCTCAAAAAGCGTGGGTTTGGGGG  
GAAGTTGCAGTCATCCTAACACTTTACTCCTAAATACTTATACATGTAATTCCTAAGAACAAGGACATTCT  
CCTATATAATTACGTTACCATCCTCACATTTAAGAACGTTAATTCATAACAATATGTAGTATTCAATCAA  
TGTTAAAAATTTCCCAAGTCCCAAGAATGATTCTTCCCCCTCAGGATTACACACTGCATTGTTGTTAT  
GTGCACTTGGTCTTGTACAGTGTGGAATAATCCCCAACCTTTTTATTGTCCAAGACATTAACCTTATCAAG  
AGTCTA

The following amino acid sequence <SEQ ID NO. 143> is the predicted  
amino acid sequence derived from the DNA sequence of SEQ ID NO. 15:

LGICSFHFSYCLTSLLYFLLSFFTFQSSLIHSLAGFNALPYSLSFLNKYLNIFYVTFKHFLCNLLLTHTEI  
LLKVLSCYILKVSVCSLFFPRDNCFFTFYISFFLCFQFFQLYYKKFQTNENLNKWYNHRNFRFDYLFVFAF  
LFLCMLISITPFEVKFPSNQKNSGYFIGRGTGEPKASGNVLHNLHGSYTCCKNSERYTSDLYPLLCISS  
ISKRRGFAGEVAVILTLYSILIHVIPKNKDILLYNYVTILTFKNVNSITICSIQSMKLISQVPRMILPPSG  
LHTAFGCYVHLVLYSVESPTFLSKTLTYQGV

The following DNA sequence Seq-2474 <SEQ ID NO. 16> was identified in  
*H. sapiens*:

CCAGGCAGAGGAACTGTAAAGTCAAAGACTAGGGTAGGGGAGGAAGGATAAGCAGAAAAACACTGAGAAT

TTATATACTGGCAAGAAACCCAGGTGACTGGAGCAAAGCAAACCAGCAGCGAGCGGATGGCATGGAGGCTG  
GAGAGCCAGGCAGGGGTCAAAGTCCCCGTGCAAGGAGCTTGGCTGTCATTCCATGGGCTACTGGAGAGAGA  
AGCCGTGGAGCAATGGGATCCGATGTAACTTGAAGAGATCACTCTTACTCACCAGTGAACTGAGTGAA  
CTACTCACATGCTCAGCCATTAAATGGATCTAGAGGGAATTATGCAGAGTGAGAAAAGCCAATCCCAAAG  
GTTATATACAGCATTGATTCCATTTACACGACACTGTTGAAATGACATTGCAGAAATGAAGAACAGATTAG  
TGGTTGCTGGTAGTTAAGGAGGGGTAGAAGCATCCGGACGGTGGTTATGAAAAGCCAACACAGGGATCCCT  
GTGGTAATAAAGCCGTTCTGTAACCTCCTTGACTTTGTCAATGTCAGTATCCTGGCTATGATCCTGTACCA  
TTGTTTTGCAAGATGTTACCACTGGGGGAAGTGGTTAAAGGGTATACTCTTCATATTATTTT

The following amino acid sequence <SEQ ID NO. 144> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 16:

EEIRVYPLTSSPSGNILQNNGTGSPGYHQSGSYRTALLPQGSCLWLFITTVRMLLPLLNYQQPLICSSFL  
QCHFNSVVMESMLYITFDWLFLSLCIIPSRSIKWLMSVSVSLVSKSDLFQVNIGSHCSTASLSSSPWND  
SQAPCTGTLTPAWLSSLHAIRSLLVCFAPVTWVSCQYINSQCFSAYPSSPTLVDFDTVSSAW

The following DNA sequence Seq-2475 <SEQ ID NO. 17> was identified in *H. sapiens*:

ATGATTTTTTATTTGAAAAGTCACATTGCACAGAGTGATATATAAATGAATTTTCTGAAGATATATGTGTTA  
AATCAGGGCTTTTCAGGCACAGTCTGCTTAAACTTTGGAAAGAGATACTATTTTTTTTTCAGTGCATTGTGTA  
TCTTCTAATTTTCTCATAGTAATATCACAGGGTCCCCATAGGTGATGCTGAATATGGGCAACTGGTTTTTTT  
TTGTTTTTTTTTTTTTACCTGTTGTCTTAGCATTCCCTAAACAGGGGTCACCAATCCCAGGCCACCTAG  
TGGTTCTGGTCCATGGCCTGTTAGGAACGA

The following amino acid sequence <SEQ ID NO. 145> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 17:

FLFEKSHCTEYINEFSEDICVKSLSGTVCLKLWKEILFFFSAFVSSNFLIVISQGPHERCIWATGFFCFFF  
FTCCLSIIPNRGHQIPGHLVVLVHGLLGT

The following DNA sequence Seq-2476 <SEQ ID NO. 18> was identified in *H. sapiens*:

AAGACTCAAGATACCATGAATTAATCCAAGTCTCAGAAAATAATTAAAAAAGACAATCCCGATGA  
GGTTACAGGACACAAAAGATAACATGAGTCATCACCGAATAAGACTAGGAGGCCTTCCGGAAAGGGACAAT  
TGGGGGAAAAGCTTGCCAAACTCTTCATTAAACACAGT

The following amino acid sequence <SEQ ID NO. 146> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 18:

TVFNEEFWQAFPPPIVPRKASSYSVMTHVIFCVLPHRDCLFFFLFSETWINSWYLES

The following DNA sequence Seq-2477 <SEQ ID NO. 19> was identified in *H. sapiens*:

TTGTCTGCTTTGTGATCATCAGCTTCTTCCTTTGGGTCCTGCCCTTAGTTGTCCTTGTGTGCCTGCCAGGA  
AAGTTTCTGACCTTTGCCCTTTGACCTCCTGTTGCTACTGTCCATTGTGGTCAGCATGCCCTCACCTAGTCAT  
CTACTTCTTGGCTGAGTAACTCTACAGGAAGAGGCACAGGGAGTCCCTAAAGGCTGTTTTTTCAGAGGGCTT  
TGTTGAGTGAGATGGAGGCATGGATAAAATGAGGCGTTTCAGGCCCCCGATCCCAGGGCAGATTTTCAGCCT  
CACAGCTGGAACAAACTGCTCTTCTAGGGGGCTCAGCTCCTCCACAAAGGCAGGGACTGCCTATGCACAA  
GGCTGTAAAAGGGATCATGTCTGGAACATGCTGAATCCTCCAAGGAGCAGGGTGAATGTTCTTGAGATT  
ATTTATTACCTTTGTGATTTTTCAGAGTAACCAGATTTCTGACTGAATTCAAGACAAAATTACTTTGCTTC  
TGTTGATAGCCCATTTCTCAATCCCATGGAAACCTCTGGAAAGGCAGGTGAGGAGCAAAGCAGACCT  
TCCTGGCTTCTTCTTTTTTTTTTTT

The following amino acid sequence <SEQ ID NO. 147> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 19:

VCFVVISFFLVWVLPVVLVCLPGKFLTLAFDLLLLLSIVVSMPLVIYFLAELYRKRHRRESLKAVFORALL  
SEMEAWIKGVSGPRSQGRFQPHSWKQTALLGGSAPPQROGLPMHKAVKGIMSGKHAESSKEQGECSDYLLP  
LCIFRVTRFLTEFKTKLLCFPIILNSHGNPLERQVRKADLPGFFFFF

The following DNA sequence Seq-2478 <SEQ ID NO. 20> was identified in



*H. sapiens*:

CACGGCTAATAATTACAACACAGTGTCTGCTTTCTGGACAGCACAAAATACAGCTTTTCTGCTTTT  
TGTAGCCACATTCTCATACCTCCCTTCCCAACACAGAGAACAGTATAACAGAATACTGGGAACACAATTA  
GGAAATGAAATTAGAAAAAGGGAGCATCAGGTAAAGCAAGCATTTAAAGAAGCCAAAAGGCTTTCTCCTA  
ACAAGAGGCACAAACGCGTGTGAGCGGCCGGCGAGTCCGAGCTGCACTGCGGGGCCGCTACCTTCAGACTT  
CCCTGTACGCTCCACACTTCCACAACGGGCGAGGCTACTTTTATAATCATAAAAAATGCCCAATCAATACA  
ATTTTCAAAAGAAGAAGCGGAAGGGAAAAACCAATC

The following amino acid sequence <SEQ ID NO. 148> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 20:

IGFSLPILLLKIVLIGHFLLKPRPLWKCGAYREVRPRSAARTRRPLTRVCASCEKAFLASLNACFTCSLF  
LISFPNCVPSILLYCSLCWEGRYENVAYIKTAESCILCCPESRNTVLLAV

The following DNA sequence Seq-2479 <SEQ ID NO. 21> was identified in *H. sapiens*:

CTTTGACATTTTGTATAAGCTGTAACCTATATGTCTCCTTATAAATAACATTTCTTGACTGCCAGCTTTA  
CTGATCGAGGATTGGATTATATTTTAAACATATCATGGCGTTGGTTCCAAAACAATGGTCAAAGCAGCTTG  
CCAAAAAATAATACCAAGAGGGATATATCCTGATTGATTCTCACATTCCTCTCAGATACATTGGTAAATG  
TGATATACTGGTCTATAAATGTACTGAACAACGTGTGACAGAAACCAGGCAGGGACATTCTGAAGGCAG  
GTTGCCGACAGTGTCTATAGCCACATACCTGATATGCAACAATCTGCATTCTATTCTGATTGTATCAGGTGA  
AAGCTATG

The following amino acid sequence <SEQ ID NO. 149> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 21:

LSPDITIRNADCCISGMWLTAATCLQECPLVSVTRCSVHLDQYITFTNVSERNVIRINQDISLLVFFFWQ  
AALTIVLEPTPYVNIQSSISKAGSQEMLFIRRHIGYSLQNVK

The following DNA sequence Seq-2480 <SEQ ID NO. 22> was identified in *H. sapiens*:

ACTAGATGGTTCCCATGTGCGCCATTAAGGTAGTGCAGGTTAAATCCACACACAACACTAGGTGTGGTTGTT  
CATGCTTTCCCATACTCATCAGGAGATCAGAATTGTATAGGTCCTGTCCGAAGAGGTACCTGGATTTTGA  
GTCAAACAAACCTTGATTCTCTCATTTCCCTAGTTGGGTGACCTTGAGCAAGTAAGTTAACCTTTCTGAGTC  
TCAGCTCATCTATAAATGGGAAAACCTACACCTACTTCATGGGACTGCAATTAGGTTTAAAGATAATGGTT  
ATCAACAACCTAGTCCAATATTTAGTATATACTAAGTGCTCAATAAATGCTACTGCTATTTGCTCCTCTCA  
TCCTATTCTTTCTTTGTGGATAATCGGTTCAATTCTCTCAGCATCAAACCAGGTAAGAAAAGGGATGAGC  
ATCGACCGTGGAGCCGGTCAATAAAAGACAGCAAAGGCTTCTCCTCTGGCCACCCCTTCCCCATGTGTTGG  
CCCAATCATGTCCCACTTTGGTCTCAAGGTTATAGTATGGGCTGTTCAATTCCACAAAGGCCAAGTTAA  
TATCTGACCAACCCCAAGTAATTAATGAGTACTGGCCCTGTTGGCAACTCTGTTGCTGGACAGGCCTTGT  
GTTCAAGTTTCAGCGCATGGACTGAGCACGCACCCTGATCAGCCCCCGTCTCACTGCTTTCTTACATCAA  
ATCCTCACAAGCAACCAACCCG

The following amino acid sequence <SEQ ID NO. 150> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 22:

MVPMSPRLRCRLNPHTTLGVVVHAFPYSSGDQNCIGPVRRGTWILESINKPFSHFLVGPASKLTFSLSSSIK  
WEKLHLLHGTAIREFKIMVINNLVQYLVYTKCSINATAICSSHPILFFVDNRFNSLSIKPGKKRDEHRPWSR  
SIKDSKGFSSGHPFPMCWPNHVLWSSRLYGLFNSTKAQVNIPTPSNMSTGPGVNSVAGQALCSVSAHGLS  
THPDQPPVLTAFHLQILTSNHP

The following DNA sequence Seq-2481 <SEQ ID NO. 23> was identified in *H. sapiens*:

TCATTAAATCTCTTATTACTAGTCTAACTCTTCAGCCCCAAGACTGTCTTGAGGAGTTCGAGTACCACGG  
CATGGCCAAGAGGCCAGCCAGCAATGATATCTGTCTTCTAAGCTTTGATTTCAGCCTTATCTGAGAAGT  
TGAAGTGGGGGGTAGGGGACACTCCTGCTGCCAACTGCCCCGACTCACCAGTGATGAGGTTGTCAAAGGG  
TTGGTGGGCATGCAGAAGATGCCACCAGCAGGTCACTGACAGCCAGGTTGAGGATGAACATGTTGGTGAC  
AGTATGCATGTGCCGTTCTTGAGCACGATGAAACAGACCAGGGTGTGCCCCACCATGCAGAGCAGGAAGA  
TGAGCGCATAGGCCACAATGAACATGGCCGCCACAGGGGAGGTGTGCTGATAGTAGGAGGAGAAGGTGAGG  
TTTGTAGCCGGGTGGCCTCAGTGTTAGTCCCATCTGACTTAGGGGCCAACTGCTGTTGGGAGGCTGGGA

GGGCTCCCCTAGGACCAAAGGAATATATTGGTCAGGACCTTAAGCAAAGAAGAGATTACCGATTCTCACC  
ACTAATGAGACCCTCTGTGTGCCAAACCTTAACCATGCCCTGGTCCCCCAAGCATG

The following amino acid sequence <SEQ ID NO. 151> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 23:

MLGGPGHGGGLAHRGSHWEIGNLFFAGPDQYIPLVLGEPSSQPPNSSWPLSQNGTNTTEATPATNLTFFSSYYQH  
TSPVAAMFIVAYALIFLLCMVGNTLVCFIVLKNRHMHTVTNMFILNLAVSDLLVGIFCMPTNPLDNLITGE  
CGQLAAGVSPTPHFNFSKAGNQSLLEDYHCWAGLLAMPWYSNSSRQSWGRVRLVNKRFN

The following DNA sequence Seq-2482 <SEQ ID NO. 24> was identified in *H. sapiens*:

ATGCTTCATTTGAAAGTTACCAAACCTGTGTGTGCACATACACATTGCAAATCCTCCCAAACCTGTAATGTC  
TCTGCTATGGTTTGGATATGGTTTGTTCATCCCCACCAAATTCACATTGAAATTTCTTCCCAAGTGTAGT  
AGTGTGGGAGGTGGGACCTAGTTGGGGAATGGCTTGGTGCCACTCTCTAGGTAGTGGCTGAGTTCTTGCT  
GTGGCGAGAATGAATTAGTTCTTGGCGGAATGAATCTTAATAGTTCTCTGCCAGAGTGAGTTTTATAAAG  
CCAGGATGCCCTTGGGTTTGTCTCTTTTACATGTCCACTTCCCTTTGACCTTCTCTGCTGTGTTTTG  
ACCTAGCATGAGACCTTACCAGAAGCCAAGTAGATGTCAGCACCGTGCTTCTCTAACTTTCCACCTGCAA  
AACTGTGAGCTAAATAAACCTCTTTTCTTTATAAATTACCTAGCCTCTGTATTCTGTTATAGCAACACAAA  
ATGGACTAAGACGGTCTCCCAAACCAACTGTGGGCTTTTCTTAAAGGTCACCCCGACA

The following amino acid sequence <SEQ ID NO. 152> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 24:

MLHLKVTKLCVHIHIANPPKLMSELLWFGYGLFIPTKIHIEISSPVCWEVGPWSGMAWCHSLGSGVLAVARM  
NFLREILNSSQSEFLSQDAPWVLSLFTCPPLSLPSLLCFDLADLHQKPSRCQHRASLTFHLQNCLELNKPLF  
FINYLASVFCYSNTKWKTKTVSQTNCGFLFKVTP

The following DNA sequence Seq-2483 <SEQ ID NO. 25> was identified in *H. sapiens*:

CTTAATACAGAATGATGTCAGCATGAACCAGAAGTCATGTTGGTTTCATGGGAGATTTCTTTCCAATGTTAT  
TTTGAGTCACCAAGTAACAGCAGCCATGAGCAAGATACATAAATACAGTGCATGCAAGCCCAAGAGGCCTG  
TAGTACTGCATCCACATGCTTTCTTTTGGTTGGTTACATGTTCTGTCTTGGAAATTAAGTGTGTTA  
TTGTACAATCTTCTGGATCCTTGAGCATTGTCCTTGCCCTTGCAATCCAAATGGGCAGCCTCAACCTTACAT  
CAAGTTTATTTACCTGTAACTCTGCTAGCATTGTTAATTTTACTGCTTTTCTGAGTGTGCGCTTATCA  
AGTTCAATATATTTGAAGTGGACTACCTTTACCTTATTTCCCCCCCACCACAAAAGCCCTGCAACTTTTA  
CTGTAGTATTCTGCTGAACACAGGTGGGAACACAGATGTCATATTACAGCAGAAATATCTATTCTTGTGAG  
GACATCCTGACAGTGACATGAAGTGACACATTGTGCATACCACTATAGCACATCGTTTCCACAGGAAA  
TGCTGCAGACAGTGATGAGGGTCCAACAACCTCAAGGCTAAGGGTGGCGGGTGCTAGACAGCTCGCTAAGC  
CCCCTGCCAACTCCCTTCCATGTACCTGCTTCACAACACGAAGCTGCTTCACAACAGTGCCAACGAACAAC  
TGATCGACCAAGGACAAATCACTGAATTCATCCGTGGAAGCGAAGCTCTGTGTACTACATGTAAAG

The following amino acid sequence <SEQ ID NO. 153> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 25:

LNTECQHEPEVMLVHGRFLSNVILSHQVTAAMSKIHKYSACKPKRPVVLHPTCFLFVWFGYMFCLGINCLL  
YNLPGSLSLPLHPLKLSLNPYIKFISPVNSASILIFTAFLSAALIKFNIFEVDYPLPYFPPTTKALQLLL  
YSAEHRWEHRCHITAEISILVRTHPDSDMKHIVHTTIAHRFHQEMSADSDEGPTTPSGWRVLDSSLSPLPT  
PFHVPASQHEAASQQQRTTDRPRTNHIHPWKRSSVYYM

The following DNA sequence Seq-2484 <SEQ ID NO. 26> was identified in *H. sapiens*:

GAAAGCTTAGCCCATGATGGTGAGGTAGTTCCCTTTGGTGAAATGTGAACATTAGCCATTTAATAGTTTCAT  
TTCCTAAAGTCTAAGTATATGGATAAGGTCTATGCTTTCCACAGAGGTGTACAGGTGAAGGTGAATCAA  
GTTTGCTTACAAAATTTTTTAACTATGACCTTGCGAGAGATGTAGTTGTAATAGAAATATATCTGGA  
ACTGTAAAAGCAACTAAATGTATAATTATTTGGCTGTTCTTCTGCTCTTTCTCTGACTCTTCCCATATCT  
GGATCCTTCTTACTCATTGGATTTTACAGACAAAAATGCTTTCTCAGAGATGGCTTTTGTGTTTCATCTGTT  
TAAACGCAGTCCCCTTCTTAGTCTTGTCTCTTCTAACAATACCATGTTTACTCATGCTATGGTTTG  
GATATGGTTTGCTGTCCCCACCAAATCTTATGTTGAAATAATGATCTCCAGAGTGGTGGTATTGGGAGGT  
GGGGCCTAGTGAGAGGTGTTGGCATCATGGGGGCGAGATCCCTTGTAATGGCTTGGTGCCATTCTCATGGG  
AGTGAATGAGTTCTTGTCTTTTGGACTGGGTGCTTCTTGGGGAAAGGATTAGTCTCCCTCCGAGTG

GGTTGGTATAAA

The following amino acid sequence <SEQ ID NO. 154> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 26:

KLSPWGSSSLWNVNISHLIVHFLKSKYMDKVYAFPTVEYRQVIFKIFLNYDLGRDVVIEIIFWNCKSN  
MNYLAVLPALSLTLPISGSFLLIGFQDKKCFLRDGFVHLFKRSPLSSCHLLTNYHVYSLLWFGYGLLV  
TKSYVEIMISRVVVLGGGAEVLASWGQIPCKWLGAJLMGVNEFLLFDWVASGKGISLPPSGLV

The following DNA sequence Seq-2485 <SEQ ID NO. 27> was identified in *H. sapiens*:

GTTAGTGGGCATTTTTTTTGGAGCTGTGGCTTCAAATGAGTTTCAACATAAACTACTTTGAATAGTTGA  
TAAAATGGCAGTATGTGGGTTTACATATTGATTGGTCGTGCTGATAGTCTTATTAAAGCAAGGCTGTAG  
AGGCCAGGTCACATTCTTTCCATGACATTTTAAATGAGCAGTTTAGGGAGGGTGGTGGCGTGGTGATTGTA  
AGTGGGGACAAAGTGGCAAAGATTAACTCAGTATTCATTTTGCCTGACTGCAGAATTTAAATAACCCTTCCA  
CTTGTGCTGGTACTGTCAACACGTGGTAGAAAATATAAATTAGATTGTGCTCTACACAGACTGTATATAA  
TAATTC

The following amino acid sequence <SEQ ID NO. 155> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 27:

VSGHFFWSCGFKVSTLLIVDKNGSMWVYILIWSCSYSKAVEARSHSFHDILMSSLGRVVGVVIVSGDKWQ  
RLTQYSFCLTAEFKPFHLLLVLSTRGRKYKLDLALHRLYIII

The following DNA sequence Seq-2486 <SEQ ID NO. 28> was identified in *H. sapiens*:

GCACCAGTATCTGTCTGATGAAGCCTCAGGAAGCTTCCACTCGTGGTGGGAAGGTGAAGGGAGCTGGCAT  
ATACAGAGAGCACATGGTAGGAGAGAAAGGCAAGGAGAGAGAGATGGTGCCAGGCTCTTTTCAACAAC  
CAGTTCTTGCAAGAATTCATCTCATGAGTATGGCACCAAGACATTCATAAACGATCCACTCCCACAACCC  
AAACAGCTCCCAAGCCGTACCTCCAATACTAGGTGGGCATCAAATTCACATGAAACTTGGTGGGGC  
CACACAAACCATATCCGAACCATAGCAAATGTCTTGAAGGTAAGAATTCTCTACCACAAGCTTCTCTGCTG  
GGTACATATGCTCTGCCATAAGCAAATCTTGGGTGAGCACTGGTGAATAACCAGCATCACAGAAAGAAA  
GACAGATACCAGGGCCCTGTTACCAACAGCCTGGCAAATAGATGACCACACTGGATCTCAATTTACAAAAT  
GGGGGTAACCAGGTGGCCTAGATAAATCTTGATAGATATACAGAGAGAGGTAAAGTAGTG

The following amino acid sequence <SEQ ID NO. 156> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 28:

LLYLSLYIYQDLRPPGYPHFVNDPVWSSICQAVGNRALVSVFSFCDAGSPVLTQDLLMGRTYVPSREACG  
REFLPSRHLLWFGYGLCGPTKFHVIGICPPSIGGTAWWELFGLWEWIVYECLGAILMRVNSCKNWLLKRAWH  
HLLSLLAFLSVHLSVYASSLHLPFRVEASGFIRHRYWC

The following DNA sequence Seq-2487 <SEQ ID NO. 29> was identified in *H. sapiens*:

TTCACCACAATGAAGAAAACAAATCCTCTTATGAACATGATCTCATTAGTTCCCATATGACACATTATTC  
TGACACGAAGCGAGGTCTAAGAACTTCAATACTCACTCTCTTTACAGATGGGGAAAGTGAGTCAAAATTC  
TGGGAAGCAGCAAAGCAATTATCCAAGCTGGAATTAAGCCTAGCGTTCTAAATGCTCATTAGTGCTAGT  
GCTACCCAAAATGATTCTACATTTTATAAGCAGGTAATAAATAAATAAATAAGCAGGATCAGCCAGGAT  
GAAGTGAAATAAAAAATAATCCATGGAGTTTAAACAGCTTTTCTGTAACCTTTGACTGCAGCTCTTTGCC  
TGAAGTGTAACATACAAAACAAAAGAGAGTAAACAGAGCATACTGAAATCTTGACACCTCTCAAAGAAC  
TAGATGGTTTACCTTTTACATAGGAAGCAAATAAAGGAGAACTGTCAATGACTGATGGGAACACAGTAC  
AAAATTTAAGTTAGTGGTTTATTTTAAAGCTTGTATAATATGGACTACAAAGGGCATTTTTGAAGCCATGC  
AAAGGTCACCCACACACTAGTCCCTTCAAACCTAGCTTTTTTC

The following amino acid sequence <SEQ ID NO. 157> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 29:

KKLVRDCVGDLCMAQKCPISILYKLTNNLNFVLCSSHQSLTVSPLFASYVKGTIFFERCQDFSMCLFTLFW  
FCMLHFRQRAAVKSYRKAVKTPWNYFYFHFILADPAYIYLFITCLNVESFWVALALNEHLERALIPAWIIA  
LLLPRILTHFPHLREVLKFLRPRFVSECVIMGTNEIMFIRGFVFVIVV

The following DNA sequence Seq-2488 <SEQ ID NO. 30> was identified in *H. sapiens*:

GCACCAGTATCTGTGTCTGATGAAGCCTCAGGGAAGCTTCCACTCGTGGTGGAAGGTGAAGGGAGCTGGCA  
TATACAGAGGAGCACATGGTAGGAGAGAAAGGCAAGAGAGAGAGAGATGGTGCCAGGCTCTTTTCAACAA  
CCAGTTCTTGCAAGAATTCACCTCTCATGAGTATGGCACCAAGACATTCATAAACGATCCACTCCCACAACC  
CAACAGCTCCCACCAGGCCGTACCTCCAATACTAGGTGGGCATCAAATTCCAACATGAAACTTGGTGGGG  
CCACACAAACCATATCCGAACCATAGCAAATGTCTTGAAGGTAAGAATTCTCTACCACAAGCTTCTCTGCT  
GGGTACATATGTCCTGCCCATAGCAAATCTTGGGTGAGCACTGGTGACTAACCAGCATCACAGAAAGAAA  
AGACAGATACCAGGGCCCTGTACCAACAGCCTGGCAAATAGATGACCACACTGGATCTCAATTTACAAAA  
TGGGGGTAACCAGGTGGCCTAGATAAATCTTGATAGATATACAGAGAGAGGTAAAGTAGTGAAAGCCCTAT  
GAAAAATGTAATTCAATATGAAAACGTATGGTATTATTACTACAATGCTAATAAGCAATTAAATGTTTCTC  
AAAAATAGGGAAGACTGGGAAGAAGGAAGCATTACAAGCTAAGCTGGCT

The following amino acid sequence <SEQ ID NO. 158> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 30:

ASLACNASLLPSLPYFETFNCLLALYHTFSYITFFIGLSLLYLSLYIYQDLSRPPGYPHFVNDPVWSSICQ  
AVGNRALVSVFSFCDAGSPVLTQDLLMGRITYVPSREACGREFLPSRHLLWFGYGLCGPTKFHVIGICPPSIG  
GTAWWELFGLWEWIVYECLGAILMRVNSCKNWLLKRAWHLLSLLPFSPMTMCSSVYASSLHLPPEASLR  
LHQTQILV

The following DNA sequence Seq-2489 <SEQ ID NO. 31> was identified in *H. sapiens*:

TTGATTCTGTCTTGTGGACACAGAAGAGGCTGCCAGCTGAAGAGAGACATGTCCTCAGCTTTTCTGGT  
GAGTGAAGGCCTGTGCTGGAACCTTATGACAGCAAATCCCAGCTCTGAAAGTGGATTTCTATATCTTCCTCT  
TCAAACCTACCGTCACTCTAGAGAAAGAACTCTTCTTCTGTGTTTTATTTATGTCTAAAAACATAGGTAA  
ACGGTGTATGTATGATGTCTTCTTATTTATTTCTTTCTTCTAATTGCAAAAAATCACACATGTTCC  
TTGTAAAAAATCAACCAACCAACCAACCTTGAAAAACTTAAACAATGAACAAAGAGAAAAGAAATACCT  
AACATCAACATAATGTGTATACATTACAAAAGCTTGAAAAATACAGAAAAACACAAAGGAAAGAAAAA  
AATCACTTCCACTCAAATATTTCTGTTAATTTAGTATATAGCCAAGCATTTCCTCATGTAT

The following amino acid sequence <SEQ ID NO. 159> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 31:

FLSCWTQKRLPSRETCPQLFWVKACAGTYDSKSQLKWISISSSSNSPSLRKNSSFLCFIYVNIKRCMYDV  
FFLFISFCNSCKSHMFLVKSTNQPTLKNLNNEQREKKLPNIKHNVYTLQKLEKYRKTQRKEKITSTQN  
YFCFYIAKHFSMY

The following DNA sequence Seq-2490 <SEQ ID NO. 32> was identified in *H. sapiens*:

ACTTTGTCAAAAAGTACAGAGTATGAACCTCACAGGGAAAAGCCCTCTGAAATCGACCTGCTGGTTAGGG  
AATGAGAAGGAGGTAGAGCCAGGCAAGGCCACTCCTTCTGGGTACATAGGGAAAGAAATTAAGCTGCTAC  
AACTAGACAGTCAGAAGTTGCTCAGAAGTGGTAGTCTAAATGTTCTTAAGGGAGCTACTCTGGTTTGTT  
ATGGTTTGTCTGTCCCCACCAAACTCATGTTGACATTTTCTTCCCAGTGTGGCAGTGTGAGAGGTGAGG  
CCTAGTGGGAGGTGTCTGGGTATGAGGTGGATCCCTCATGAACACTTAGTGCTGCTCTCAAGTTAGTGA  
GTTCTAGCTTTGGCAAGACTGAATTAGTTCTTGTGGAAATGGAGTAGTTTCCTCGAGAGTGGGCTGACATA  
AAGCCACATGCCCTTCACATGTGTCCACTTCCCCTTTGACCTTCTCTACCATGTTCTGGCAGCACAGAAGC  
CTCACCAGAAGCTGAGCAGATGCTGGCACCATGGTTCTTATACAGCCTGCAGAACAGTGAGCTAAATAAAT  
CTATTTTCTTCATAAATTACTCAGCCTCAGGTATTTTTTTTTTTTTTTTGTAGACAGAGTCTCGC

The following amino acid sequence <SEQ ID NO. 160> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 32:

FVKKVQSMNLTGKSPLKSTCWLGNKEVEPGKATPSGYIGKEIKAATTRQSEVAQKWSMFLRELLWFGYGL  
SVPTKPHVDIFFPVWQCEVRPSGRCLGHGGGSLMNTCCSQVSEFLWQDISSCGNGVSSRVGHKATCPSHV  
STSPLTFSTMFWQHRSLTRSADAGTMVLIQPAEQAKIYFLHKLLSLRYFFFFFLRQSL

The following DNA sequence Seq-2491 <SEQ ID NO. 33> was identified in *H. sapiens*:

CCAGTGTGGCTGAGACAGTGAAGTAGGTGAAGGGTAAATGAAATGAGGTTTGGGTAGGTAAGGAGTGGT

CTGGTCATGATAGACTTTGGAATCTATTTGAGGTGAAGTTGGAAGTTTGAAGAATTTTAACCAAGCCAAT  
GGATTTTTATTATTTATACTTATTAAAGATTATTTTGACTGCAGTGTGGAGAATAGAGTAGAAAGAAATAG  
AGAAGTAAGGAACCTACTGCTATTTACATGAAAATGATGTATCATTAATGTCTTTTATCTGCATGGGGGC  
TATGCAGGGGAGAAGTGGCCAAATATAAGATATAAACGGGAGTATACATGCCAGGACTTGTGTATGGATTAC  
ATACTAGTGTTAATAGTTAACCTTCAGTTCTTGAATGGGGAACCTTTACTTATGTATGCAGTATTTATACA  
TTATTCTAGATGTGTTTACTACAAATGACAGAAATTTAATTAATGCAATTTGATAAAGAATTTACTCA  
TAAGTCATATTGTCTCATATGACTGGGAAATCTAAGGGTGAGTTAGGACTTTAGGAAAAGCTGTATCCCAA  
GCCTATAGATGACTTCTGAACCTAGTATTAATTT

The following amino acid sequence <SEQ ID NO. 161> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 33:

QCGDGSRRVKNEVWVGKEWSGHDRLWNLFVVKLEVLKFNQANGFLLFILIKDYFDCSVENRVERNREVR  
NLLLFHMKMMYHCLLSAWGLCREKWPNIYKREYTCQDLLMDYILVLIVNLQFLNGELLLMYAVFIHYSRC  
VLQMTIELKCNLIKNNLLISHIVSYDWEIGVRTLGKAVSQAYRLLNLVLI

The following DNA sequence Seq-2492 <SEQ ID NO. 34> was identified in *H. sapiens*:

GGTTGGTAGCTGCCGCCCTGCACACCAGATTGCCTCCACCACAGGGGGTTCGGACTGCTCCCCCGCCCCA  
GTTTCAGCAACTATAAGAAACCATGGCTGGCCGAATCAGAGGCCGAAGGCTTACTGTTCTAAGACTTTTGG  
AACTATCTGTTTATCCCTACTTTTCCAACTACATTGTGTATTACTCCTACTGGTGTAAATATTTACCA  
AAGAAAATTTTTCACCTTAATATC

The following amino acid sequence <SEQ ID NO. 162> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 34:

LVAAALHTRLPPPGVFPDCSPRPVQQLTMAGRIRRRAYCSKTFGTICFIPYFFQLHCVLLLLLVIFKE  
NFFTLI

The following DNA sequence Seq-2493 <SEQ ID NO. 35> was identified in *H. sapiens*:

CACTCCAGCCTGGGTGATAGAACGAGACTCTGTATCAAAATAAAAAAAGAAAAAAGTTATGCTTG  
TAGAAGCCAACTCAAGATTAATTTACATATTTAAAAATATTTTCCTTGAAATTTAATACACATCCAATAT  
CGATTATCTTCTTAAGTACTTTGTATCTTATCTTCTGTCAAGCTTGCAGTATAAAGGTGATGTCATG  
CTTTCTGCATGCCTCATGCAGGTGGCACCTCCTCCTACCCCCACGCTTTTCCAGGTGAGCCGCGAT  
GCGCAAAAGGTTGGGATGCCTGGCACAGGATGCCAGTATGTCATGCTTTAGAATGCCCCGCTGTCTCT  
CCCCGGGGCTAAATCCTATTCCACCGTGAGCCTTCTTGACCAGCAGAGAATAGAAGCGCCTGGTGCATACA  
GGCCACCAAAGGTATCTGTTGAACAGACATGCACACGGCTTCTGCCGTGGGC

The following amino acid sequence <SEQ ID NO. 163> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 35:

TPAWVIERDSVSKKKRKKVMLVEANSRLIYIFKNIFLGNLIHIQYRLSSLSTLYLILPVKLCTIKVMSCE  
SAMPHAGGTSFLTPTSFPGEPRCAKGDWHRMPASRCLNAPAVSPGAKSYSTVSLPPAENRSACIQA  
GICTDMHTASAVG

The following DNA sequence Seq-2494 <SEQ ID NO. 36> was identified in *H. sapiens*:

TATTTTACAGATTATGTTTTGTAATACGAGCATATTTCTGTGGTTCCATCCACTATCCCTAGTCTTCCCCC  
AAAGACACGCTGATGAATTAATTTTCTGCTTGTCATTGTAATTGTTATGTGTTGTAAGAAAATACA  
GAGGGCATTAAGAGAACCTATGAGGTAACCTTGACTTCACTTCAGGGTCTGGAAGGAGGAAGCAACAATC  
CTAAGTGAACTTGGACAAGAAGCACCCAATAGGTAGACAAAGGGATTGAGGGTATGAGTTGTTAGTGAAC  
AGAGGGAAAGAAGAGAGTGAATCACAAAAGAGAACAATTTTGGAGGCTAATTACAAGTTAGAAATAAA  
ATAATGAGTGAGTACAGAGAGATTCACTCCTCATGACTCCTCTCTGTGTCATCTCTCTAGGACATTTGT  
CATGTCCTCAAACACGATGCTTCAAAAATGCTGCTGATCTTGATCTCTTTTTCAGTAGTAACTTGGGTGA  
TTTTTATAATTTCTCAGAACTTCAAAAAGGTAGGAGAAAATCACCTTTGATGCAAATCACACAGGTAAGCC  
CTCACCTGTGCGACCAGCCTCAAGTCAGTTCCACTCTATTAGTCCTG

The following amino acid sequence <SEQ ID NO. 164> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 36:

GLIEWNLEAGRTGEGLPVFASKVIFSYLEVLNRYKNHPSYYKRDQDQOHFLKHRVGHDKCPRRDDTREES  
GVNLSVLTHYFISNLLASKIVFFCESLSSFPLFTNNSYPQSLCLPIGCFLSKFHLGLLLPPSRTLKSQSY  
LIGSLNALCIFLVTTHNNYNDKQKNFISVSLGEDGWMEPQKYARITKHNLN

The following DNA sequence Seq-2495 <SEQ ID NO. 37> was identified in *H. sapiens*:

TCTTCTGATAGCTGTCGGGGTAAATACCACTGACTGGCCTCAGAAAATCTACCCAATATGCTTAATTCCTC  
TCCTGAGCAGAGGATAGCAACACTTCAAAGATTATCCTAATTTTTTTATTTGCAAAAGTTTATTTGCAGAA  
GTTGTTTTTGCAAAAGTTGAAGAGTAGATAATCCCACTTTCCATATTCATAGTGCTCACAAGTCGATTAA  
CAAACCAACTCTTAACTCCTTTTCCAGAAAATGCTTGCATTAACAAAAGTGGAGATACTTAGATTGATT  
TGCTCCATTAGCTGGATCCATTACATATACTACTTGATATACTGTTCCCTAGTGGTTTGTATATGCCACTA  
TAGTGAAATTCAAAAAAATGTTCCAACCTATATTTG

The following amino acid sequence <SEQ ID NO. 165> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 37:

FLSGIPLTGLRKSTQYAFLSAEDSNTSKIILIFLFAKVYLOKLFLQKLKSRSQLSIFIVLTSRLTNQLLTP  
FPEKCFALTKVEILRLICSIWIHYIYYLIYCSLVVCICHYSEIQKKCSNLYL

The following DNA sequence Seq-2496 <SEQ ID NO. 38> was identified in *H. sapiens*:

ATCAATTAGGAATTCACACTCAATCAACACAACCTCAATGATGAGAATGACACTCTAAAGGACAGGAACCTT  
AACTAACTTCAAGGGACCAACACCTTTGAACAAAAAGCCACGTTATGAACCAAAAAAAAAAAAAAAAAACC  
CAAAAGTAAACGTTTGATAACAGAATGTGGTGCTGGGACATGAGGCAGACAGTAGTAATTTACAGTGTCA  
TTTATCGGTTGCCATTTACATGTCGGTTGAGTTTCTAGTATTTTAAATCAAATGTTGTTTCAAGTCATCAGC  
ACATTAGTCAATCAAGTTTTAGAGTCCTTCATTCCCAGACTCTGCAACACTGTGATCAGTCTCTCCCCATT  
TCTGGGCCAGGCAAACTCTTTGTTGATTTCAATGGGGTGATCCTAAAATCCAATCAGGCCACAAATGATT  
TGGACTGCTGCTACTTCTCTCACCTTGCTTCTTATTTCTCTCTCTTTATGTTCTCTTCTCATCTCTCATT  
TTGTTGTTCTCTCAAACTTGTCAAAATATTTCCCCTTTAGGATCTTTACATTGACTAATTCCTTCTCTAG  
AATACTCTGTCCCCCAGATATAACATGGTTTATTTTCACTTCATTTCGAACCTTCTCAAATGTCACCT  
TCTCCATAAAGCCCAATGCTAGTTATTTCTATCACTTCTAGCTCTCGGATATGTCTTTGCCCTTTAC  
TGCTT

The following amino acid sequence <SEQ ID NO. 166> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 38:

QLGIHTQSTQPOEHSKGQELKLTSRDQHLTKSHVMNQKKKKPKSKTFDNRMCWDMRQTVVIIYSVIYRLP  
FTCLRSFYFNQMLFQVISTLVNQVLESFIPRLCNTVISLSPFLGQANSLLISLGLWILKSNQATNDLDCCYF  
SHLASYFLPLYVLFILILILLFLKLVTISPLGSLHLIPLPRILCPPDINMVYYFTSEFPSSNVTFSIKPTM  
LVIFYHFLSDMSFALYC

The following DNA sequence Seq-2497 <SEQ ID NO. 39> was identified in *H. sapiens*:

AGCTCTAAATGCATAAAGGCCAGGAATTAAGCTGTGAAATTAACCCCCCAAATTACAAATAATAAAATCT  
CACATAGGTGCACGGCCCCAGCAAGCTGAGGGAAAACCAAGTGCCTGCTGTGCCTTTTTATTACTTGAGG  
TATATGGAGTCTCTAATTTAAGGCTAAATATAAAATAAAGCATACACAGCTGGACTTTCAAGTATTTTCAA  
AACACATTTAATACCTTCCCGTGAAACGCCGAGAATCTGAGCAGGCATCACTTCGCACACAGTATAAACAGG  
AGTTGGCGTGGACCGAACGTACGGGCTTCAAAGCATATTTAAGAGGGTTGAACAGGAACCTGCAAGCCAG  
AGGCCTGAAGGGATCGCAATGCTGACCTGAGCTCACAGTCACACAGTGTCTTTGCCACACAGGGCTATA  
ATAGAAACCAGCAAAGCTGGTTGACACGGCCAACACCAACAGGGTCTGCCTCTGACCGCAGCTTTGCCTGC  
CCCCACGTACTTTTTCGGCTCTGTTCTCTCACTCCAGGGCCAATGGAAAATGAGAAATATCCAAGTCTCC  
TGGCAGCCATGAATGGATTCTCTGTTAT

The following amino acid sequence <SEQ ID NO. 167> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 39:

ITENPFMAARRTWIFLIFHWPWSGGTEPKSTWGAGKAAVRGRPCWCWPCQALLVSIIALVWQRTLCDCEL  
RSALRSLQASGLQVPVQPSICFSPYVRSTPTPVYTGAQCLLRFWAFHGKVLNVFKYLVQLCMLYFIFSLK  
LETPTSSNKKAAQQALGFSLSLGPGCTYVRFYFLFGGVNFTAFALFMHLE

The following DNA sequence Seq-2498 <SEQ ID NO. 40> was identified in

*H. sapiens*:

ATATACATTTTATATTACAAATATAGGTTGGAACATTTTTTTGAATTTCACTATAGTGGCATATACAAAC  
 CACTAGGGGAACAGTATATCAAGTAGTATATGTAATGGATCCAGCTAATGGAGCAAATCAATCTAAGTATCT  
 CCACCTTTTGTAAATGCAAAGCATTTTTCTGGAAAAGGAGTTAAGAGTTGGTTTGTAAATCGACTTGTGAGC  
 ACTATGAATATGGAAGTTGGGATTATCTACTCTTCAACTTTTGCAAAAACAACCTCTGCAAATAAACTTT  
 TGCAAATAAAAAATTAGGATAATCTTTGAAGTGTGCTATCCTCTGCTCAGGAGAGGAATTAAGCATATT  
 GGGTAGATTCTCTGAGGCCAGTCAGTGGTATTTACCCCTGACAGCTATCAGAAGAAAGATGTGAAACCTTC  
 CTCGCTTCCAAACATTGTGGGATCTTTGTTGCCCTTTTGAACCAATATTATTCTTTCCACTTTGAAG

The following amino acid sequence <SEQ ID NO. 168> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 40:

LQSGKNNIGSKGATKIPQCLERRKVSHLSSDSCQGIPLTGLRESTQYAFLSAEDSNTSKIILIFLFAKVYL  
 QKLFLQKLKRSRQLSIFIVLTSRLTNQLLTPFPEKCFALTKEILRLICISWIHYIYYLIYCSLVVCICH  
 YSEIQKKCSNLYLYKMY

The following DNA sequence Seq-2499 <SEQ ID NO. 41> was identified in *H. sapiens*:

ATGGACAGGGGATCTAACCCCCAACCTTGCTCAAATTGCTGCCACTTTTGTGTTGGAAGCCAGGTATCTAA  
 ATTGCCCAGGGCTCCATATGAGTGGCTGCTCTGCTAATATTCCATGTAGCTCTGCATGTCAGACTGTAGAC  
 TGGGCTCTCCAGTCACCCCTAGCCAGTGTCTTCTGGGTTGCAGTGGTTCCAGCCTCCCTGGGATGGAGGTC  
 CCTGTGGGAGGGATGGGCCACCATCTTTGCTGTTACACAGCCTTAGCCATTGTTGCCCTTTGAGCTCTAGGG  
 ATTCTGAGGTGACTAGGGACTGGAAAAGTCCCCCAGAACAGTGCAGCTGCTCTATGGATAAACAGCCAGAC  
 TGCATTTTCACATGGGTCCGAGGTCTAGTCTCTTCCCCAGGCAGAATTCTCTGACCACAGTCTATGACC  
 ACCCCCACCATGTGTTTTCTGCTCAGCAGCAGTTTCCAACCTCCCTGGGATGGGGCTACCAGAGGGAGAGGT  
 AGGCCACCATCTTTGCTGTTTCTCAACTTAAGCATGGTGGCCTTT

The following amino acid sequence <SEQ ID NO. 169> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 41:

RPPCLSETAKMVAYLSLWPHPREVGNCCPENTGGGGHRLWSGNSAWGRELGPRTHVKMQSGCLSIEQLHCS  
 GGLFQSLVTSSELELKGNNGGCVTAKMVAHPSHRDLHPREAGNHCNPENTGGDWRAQSTVHAELHGILAEQ  
 PLIWSPGQFRYLGFPAKVAIAIARLGVRSVPVH

The following DNA sequence Seq-2500 <SEQ ID NO. 42> was identified in *H. sapiens*:

TTTCCCTTGCACTACCACTGCTGCTGAACATCCTCTTCTTCTCAAAGTCATCATGACCTTATTGTCTG  
 GGACATATTTGGCCTTGCTCTGTTTTGTTCTTTTCGTTACTTTTCATACTGTGCTTTCCAAAACACATCAGT  
 CATCTTCTCTTCACTGGTTGCATGGATGCTGGAGTCTGTGTGGCCTGTGGCAGACAACCTGTCCATCCCC  
 CCACCTTCCCTGGCTAGCAGAAGCTCTGATTTTGTAGGGATAGCAGAGTACCTGGCTAAAAGCTTGATTTTCT  
 AGGGTCTTTTGGAGTTAAGGTGGCCAAAAAATAAGTCTGGCCAATGTTTGTAAAGCAGACATCTATGGG  
 CGGGTCTTCTAGAAACGCTGTTGTTTTCTGGTAAAGCGGCCGTGTTCTTTTCATCCCTCATGTTTCTCTC  
 TTCTGGTTTGGAAAGCGGACTACACTTGCTGCCTTCCAAAAGGCAGAAGGAGCTTTGATCTTGAAGTCATT  
 GCAGACTTGCTGTTCCATGGGAAGAAGACAGACCTCTACTGGGTTAAGCCATTGTGGTTGGCTGTGTTACATG  
 CAGCCAAATATGATTATTGATACGTGAGGTGCTTCTCTGAACCTCATACTGATATGAGCCAAGCAATTTAAA  
 CATGTTTAAATGGGGCCTTTAAATGGCATCCGGGCTGGGCACGGTGGCTCACGCCTGTAATCTCAGCAC

The following amino acid sequence <SEQ ID NO. 170> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 42:

FPLQYHVLSEHPLLLKSHHDLIVWDIFGLALFCSEVTFHTVLSKTHQSSSLHHLHGCWSLCCGLWQTTLISIP  
 PLPGQNSDFVRDSRVPGKLDLFLGSFGVKVAKKLSPGQCFVSRHLWAGLLETLLFFWSGRVLFIPVSLFWF  
 GKRTTLAFAQEAGALILKSLQTCCSMGRDLYWVKPLWLAVLHAAKYDYYVRCFSELILIAKQFKHVWGL  
 NGIRAGHGGSRLSQH

The following DNA sequence Seq-2501 SEQ ID NO. 43> was identified in *H. sapiens*:

TTTGTGGCATTTTCGATATAAAATACCGAGGGCAGTATCAGGAAGTATGCCTTGCTGTGGATGGAGAGCG  
 TGCAGTGCCGCCTCATGGGGTTCTGGCCATGCTGTCCACCGAAGTCTCTGTTCTGCTACTGACCTACTTG  
 ACTTTGGAGAAGTTCTGGTCATTGTCTTCCCTTCAGTAACATTGACCTGGAAAACGGCAGACCTCAGT

CATCCTCATTTGCATCTGGATGGCGGGATTTTTAATAGCTGTAATTCATTTTGGGAATAAGGATTATTTTG  
GAAACTTTTATGGGAAAAATGGAGTATGTTTCCCACTTTATTATGACCAAACAGAAGATATTGGAAGCAAA  
GGGTATTCTCTTGGAAATTTTCTAGGTAAATTATATTTTTTTCATTTCTGGAAAAACATAATTTTGCTAGA  
AATACGTTAAATTTTACGCAAAGGTGGATTTGTTTGTTCAGAAAGTGAGATAACATAGTCAAGACTGTGTC  
CTTTTTTACACAAAAAAGTTTTTACTATTGTGTTTATTGAAGTTTTATTAACTTTTTATTAGACAATATT  
TAGTGTGGAAAAATAAGACATACT

The following amino acid sequence <SEQ ID NO. 171> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 43:

LLAFSINTEGSIRKYALLWMESVQCRLMGFLAMLSTEVSVLLLTLYLTLEKFLVIVFPFSNIRPGKRQTSVI  
LICIWMAGFLIAVIPFWNKDYFGNFYKNGVCFPLYDQTEDIGSKGYSLGIFLGKLYFFISWKNIILLEI  
RISAKVDLFVSESEITSRLCPFSHKVFTIVFIEVLLNFLLDNICGKRHT

The following DNA sequence Seq-2502 <SEQ ID NO. 44> was identified in *H. sapiens*:

ATGCTTCATAGGATGTTTTATTGGATTACAAAGAATTTTTTAAAAAAGAATTTTTTCAAACAAGAATTTTTC  
AAAATTAATTCATTTTCCTTAATACATCCATTATTTATTTACTTTTATTTATGTTTTTCAGTTTCCTTTAATT  
GATAGAAAATTTACATGCAGTAAATGCACAGAAGTTCAGTATACAATTCAATTATTTTGGATAAAATATGT  
ACACCTAGGCAATTGACATCTCAATCAAGACACAGAACATTCTCAACACTCTGGAAAGATCCTTTGTGTCC  
ATTTTAGTTATGCTTACTCCTATCACCACCATGTTTCTGGTTTCTATTGCCATATATTAGTTTATCTTGT  
CCTTGAATTTTACGTAAATGGAATCATACACTGTGTTCTCTCTGTGCCTTCTTGAAGTCAATGTAACATT  
TTGAGATGCATTTTATATTACAGGATGTACCTA

The following amino acid sequence <SEQ ID NO. 172> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 44:

CFIGCFIGLQRIKRIQTRIFQNFISLIHPLFIYFYLCFQFPLIDRKFTCSKMHRTSVYNSIILDKYVHL  
GNHLNQDTEHSQHSKILCVHFSYAYSYPHQPCFWLLPYISLSCPISRKNWHTLCSLLCLELNVTFDAFY  
ITGCT

The following DNA sequence Seq-2503 <SEQ ID NO. 45> was identified in *H. sapiens*:

AATGTAGTTCTGCACCTTATGGATTATCCTTTCTTGGTGAAAATTACATTAATTAATAATCACTATTCAGGT  
AACTATTTGAATACATTTGCCTCTGTGCCAAGGAAAAATAATTACTTCCAAAATAAAAAGGTAGCAAAACC  
TCCTCCTAATCCTACTAAGATAATCAGGATTCCAGAAATGGGATTGATTATAAGCCTCCATACAACTCAG  
CATTGTCTTTTATTTTTTAAATCAGTTAGAGAAAATGCAGCTAGCTGTCTGACATTTTTTGTGTGTTTATAA  
ACAAAAAACTCACATCTTAGATCTGAGTAAAGTTATCCTCATATGGTCTCTCTCTCTCTCATTATGT  
AGTTTTTAATTTCTTAGCCAGAGGATACCTCATGTATATTATGAGATTGTCAATTTATGAGCAGATGT  
AATTTTATTTTCTGTGATCTTTCAAAAATTTTCTATGCTGGATAAACTACAAATAAACACAACTTTCTTG  
AAAGGAAAATATCTAGGATTTGTAAATATTAATTTTGAAGATGTTTCTTTTAAATATTGCTGATTCTTAC  
ACTTCATCCAAAGTACTTATTATATTTTTTAGGAGATATACAAGTTAG

The following amino acid sequence <SEQ ID NO. 173> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 45:

CSSALMDYPFLVKITLINNHYSYGNLNTFASVPRKNYFQNKVKAKPPNPPTKIIRIPRMGLIISLHTNSA  
LSFIFKSVRENAASCLTFFVCLTKKLTSIVKVILISLSHYVGFNLSQEDTSCILDLSIYEQMFYFLS  
FKNFLCWINYKTQTFKLGKYLGFVNINFEVFFLILLILTLHPKYLFLYFLG DIQV

The following DNA sequence Seq-2504 <SEQ ID NO. 46> was identified in *H. sapiens*:

CTGCTTAAACGACTCCTTACTCTGAGCTCCAGTTTTCTTAACCAGAAAATCAGCTATTGTTAATTTTACCT  
ACTTAGGGTCTCTCTCTATTTTTCTTTTCAGTTTCATGTTAATTTCTAAATTGCCATGTATAAGTAAAGGGT  
TGCAATTTTACACCATAAAACCCCTTATGTATCCAAGGTTTTTCATAGGAAATTTAGGACTGTATGATCCT  
AAATTGTGCTGGAGTACCACATTTTCTGTTAAGTAGTACTTGGCAATAAAGTATAGGAAAAAAATCAGT  
GGGTTGACAAAGAGAGGTCATGATAGTGTACCTGTAATGTAATTTGATAAAAAATGTGAGCCTGAAGTAT  
TGCAAGCATTGTTACATATAGGGGAAGACATTATGGGGGCAGAGGGGGGTGAAGATACAAAGTTGAATAA  
AACTTCTCTAGAGCTTCACAATCTAATAAGATAGGCATTTATAAATATCTCTTAAGGCGCACTTTGTAAAG  
TGCTAAAATAGTGGCACAAAGAGCTATA



The following amino acid sequence <SEQ ID NO. 174> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 46:

LLKRLLTLSSSFLNQKISYCFYLLRVSLYFSFQFMLISKLPKISKGLSIYTIKPLYVSKVFIGNLGLYDPK  
LCWSTTFSVKYLAIKYRKKSQREVMIVYLCNLIKNVSLNLQSIIVTYRGRHYGGRGGRYKVENFSRASQ  
SNKIGIYKYLLRRTLLSAKIVAQRAI

The following DNA sequence Seq-2505 <SEQ ID NO. 47> was identified in *H. sapiens*:

TTTTTAATTCTAGTAAGTTTGAAGGGTGAGAGTTTGTATGTGTGAACATTATAGAGACTCAT  
TCAATACTGTATAATTAGAAGTTTAATCAGGTCAGTGGAGTGTAACCATACACAGGAAGTACAGCTCCT  
GAGGCAATAGAAATCTTATGTAGAAATGTATACTTATTACCTAATCGAGAGTGTTGGGTTTGCAGTTTAC  
TAAAGTGTACACAGCCAATGGCTTTTATATGTTATGTGCAACTTGTGTAGCCATAAACTATACTAAAGT  
GCATAATAAGACATTCAACTACATACGGTTACTCATTCAAGTCTGTTATCGATTGAAGTGTACATAAAATG  
ACATTTGCAGGATAGTGTATCCTTTTATTTATTGTAAGGTTTCTTTGTTTATGTATCAGCACACAAAATTT  
AGTAATTAGCAATAGGTCTCAGTTCATTTAATGTGAATGAGCAAGATCTCAGCTCTTACTACATTCAATTA  
TGGTGTAAAGCTCTCTTGACCTCCACCT

The following amino acid sequence <SEQ ID NO. 175> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 47:

GGGQESYYTIECSKSDLAHSHMNDLLITKFCVLIHKQRLNLTINKRIHYPANVILCTVQSITDLNEPYV  
ECLIMHFSIVYGLNKLHITYKSHWLLYTLVNCKPKHSRLGNKYTFLHKNSIASGAVLPVWFTLHPDTSNYT  
VLNESLCSHINKLSPFNFSYNK

The following DNA sequence Seq-2506 <SEQ ID NO. 48> was identified in *H. sapiens*:

AACCGCACTTTTGTACCACAGGGACATGCCAGGGAATAGCTCACATCAAATGCTTTCGGGAGGGGTGCCTA  
TGAGGAAGAGGGCCGAGGTCAGCCAGACAGCTCAAAGGTACCATTAAGATGATGGACGCCTTTTCTCTGG  
TGCTTGGGCAGGCTGCTGAGCTTCATTACTCATCTCTTCCGCAGGGAGGTCACCATGCAAGGGGGTGTCT  
TGTGCTCCTCTAGCCAGGATGCAAGCCCTGGGGACCAATTACATCCTTGGGAACAGAGGATGTGGGAGC  
AGAAGTTCAGATGCTCTAACTCAAAGGGAGCCTGGCCGCTCAGTGTGTCCCTGCCTGAAAGCAGGGCTCAG  
GCTAAATGAACACAGGCCCTTCCAGGCCACTGTGGCAAGTCACAACCTCTCTCCCCACCACTATCACCTC  
TCCCCCATACCAGCAGATTCTTGACAGCCTGCAACTTCTATCAAGGGAAAACCGCCAAAGGCAAAGCCAG  
ATTTCTGACCAATTTTGAATGCCTGAACAGGGAAGGGCATAGTGGCTTCATGTCTATAATCCCAGCATT  
TAAGAGA

The following amino acid sequence <SEQ ID NO. 176> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 48:

TALLYHRDMPGNSSHQMLSGGVPMRKRQVVSQTAQRYHDDGRLFPPWCLGRLLSFITHLFRREVMTMORGLV  
LLPGCKPWGPHSHPWQRMWEQNFRCSNSKGAWPLSVSLPESRAQAKTQAPSRPLWQVTTSLPTTITSPPY  
QQILDSLQLPIKGPKPKAPDFPILKCLNREGHSGFMSIIPAFE

The following DNA sequence Seq-2507 <SEQ ID NO. 49> was identified in *H. sapiens*:

GCAGCCTTTTCCGCGCTTCCCGTGTCTGACTGTGCTGAGGGCCTCCTGAAGTGCAATTGGTTAGTCACGG  
TTTAGTGTCTTTACTGCAATGCTATTTTAAGATGCAATTAACGCTCTCATTGCCAAAGTGGCTGCTTCC  
TCCTGGGGGCCTCCTTCCTAACACGAAGGAGTCAGAAACCAAGGCCGGGAGGAGACCTGAGCTGAAGACTC  
ACTTCTGGAGTGGGCACACTTTGTCCCAGCTCCGTCTTCTGGAGCACCCAGGAGAGCCCGCTGCAAGAAG  
AAGCCCCACGGCAGGCCACGTGGAGGCGAATTCACCTCCTACCCAGACAGCGTGGGCAATGCTGAAACGAG  
CGTCAGCTCCGAACGATTTTAGTGAGGTTCAAACCTCCCTCGGCTGTGAGCCTCTGAATCTCTTCCACTT  
CAGCCACGGCCACTCCATGGCTAGGGGCGGGGAGGGGACACTCAGAAGTTTGGTTTCTTCTGAGGGGCCTG  
AGCACACACTCAGGATGTGAGTGGGGCCGGGAAGGGCAGCAAGTGGAGCCTATGCAGGAACACTTGTGCAA  
GGCTGCACGGTTTCACTACCACCAGAAGGCAACTAAAAATCCCCACAACCTCCAGGTGTGTCTGGCTGGTG  
TCACGGAGCCTCACACACGGCTGAACCGCTTAACCTACA

The following amino acid sequence <SEQ ID NO. 177> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 49:

AAFSALPRVLCGPPEVQLVSHGLVFFETAMLFDAIKTSHCQSACFLLGASFLTRRSQKPRPGDLSRLTSGV

GTLCPSVVFLEHPGEPAARRSPTAGHVEANSPTQTAWAMLKRASAPNDFSEVQTSPLRSASESLPLQPRP  
LHGGRRGGDTQKFGFFGAHTQDVSGAGKGSKWSLCRNTCARLHGFTTTRRQLKIPTTPGVSWLSRSLTHG  
TALT

The following DNA sequence Seq-2508 SEQ ID NO. 50> was identified in *H. sapiens*:

AAATATAACTACATAAGTATATATATGTACAGTTTAAGGAATAATAAAATGAACATCCATGTATTTCAGCCT  
TCCGTCTTTTTTTTTTTTTTAATACCTTGCTGAATTCAGTTTGAGGCTTTTAAAAATTTTATATTTTACATC  
TCTATTTATGAATGCTGTTAGCCACCTTAGGTTACTTTTTATCCCCATCCTTATCTGATTGGATGTAA  
AGTTATATTAGCATCATAAAAAGGGAGTCCGATGTTGGACATTCTTATTCTGTTGTATGCAACCTGAATTA  
TTCAGAGATTTCTAGGGTTTATCTCTCCCTAGTATGCTGCAGGTTCACTGTTGTGGATCAAACATGGATC  
ATTTTTGTTTCATTCTGCTAAATCAGTATTTATGATAATCAGTATTTATCATAAATACTGATTCAGTAAATA  
CATAAATACTGATTCAGTGGGCCCTTGAATCTAAAGATTTGTCTTTAGCTCTAGAAAACATTAATTTCTTT  
TGAGTATGACTGCCCCACATTTCTTTTGGTTTTCTCCTTGGGAAATTTGTATTAGATAGATGTTGGGAAC  
TTTGGGACATATGCCTGCATGTCT

The following amino acid sequence <SEQ ID NO. 178> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 50:

KYNYISIIYMYSLRNNKMNIHVFSLPSTFFFLIPCIQFEAFKNFIFLHLYLMLLATLGYFLSPILIFGCSYIS  
IIKRESDVGHSSVVCNLNLYSEISRVLSPMLQVHCCGSNMDHFCSCISIIYDNQYLSILIQIHKYFSGP  
LNLKICLLKTLISFEYDCPTFLFGFLLGKFVLDRCWELWDICLHV

The following DNA sequence Seq-2509 <SEQ ID NO. 51> was identified in *H. sapiens*:

TTTAATCTGGCCTATTTCTTGGCATATCAGTGTGCACTCGATAAATGTATAGTAATTAAATTTTCTTAGCC  
AGACAATTGCTTGAAGTTTAAATCCAGCCAATAAAAAATAGAAAGCTTAGTTGTTTGTGTAATGGA  
TAAAAAATGACAGCACAGGTGGTAAGCATTATATAGATCAAAGGCAGAGTTTCTGTCTTGCTATGCAA  
CACAATCACCTGAATATCTGATATAGTAACACTCTGGGTAATTCCAATATGCTGCCAAGGTTGAGAACG  
ACTCAAACCTTTCAGCACCTCTGGGTATTACTATTACATACTATAGCACACAGTTAGGTGTGTATATCAAA

The following amino acid sequence <SEQ ID NO. 179> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 51:

LIHTLCAIVCNSNTQRCKFESFSTLAAYWNPYGVFTISDIQVIVLHSKTENSATFDLYECLPPVLSFFYP  
LQQTTLKSIFILLAGFKLQAIWLRKFNYTTFIECTLICQEIQIK

The following DNA sequence Seq-2510 <SEQ ID NO. 52> was identified in *H. sapiens*:

TCTGCAAAATGCCTTTATCAAATGGCTTGCAAGATTAAGATGGAGTATTTATTAGTTAACCACACACAGC  
AAGCAGAGGGGAGTGGAAATTCATGATGTACGGGATGTCCTGCCAACACTGCACGGGATGGTCTACACATC  
TCTGATTGCAATAACACAACCACTCTGATAATATTCTGTACATGGACTCATAGCATATTTTATGGCTTACA  
AAATAATAGTCAAATGCTAATAAATAATTGACTTGAAAAAAGTGAAGACATAATATAAAGTAATACTATT  
TATTTTATTCATTGCTCTAAAATAATTTTATAAATTTGTCTACTCATGTTTCAGCAGTGAGTTCTGAGATT  
AATTTTATTTTCTTTTATAAGTCAAGACAATGGGGAATTTTAATTCTGTAAAGACTCAACATCCTTCCTC  
TCCACTTCATTTGGTAATTGTCTTCTTTTCATGACTGAATTCCTCTTAGTCTTAGCCTGAGTCCCACTTTGT  
GCTTATTCACAAATGATGTCTGTCTGTGAGGCCATTTCTTATCAGGGTCTCCAGACTATTTTCAGAACATC  
ACTCGTGTCAATTTTAGTTGCTGACAATTCACCTGAACTACAGAGTCTTTGGCAGCTGCATCAAAAGGA

The following amino acid sequence <SEQ ID NO. 180> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 52:

LLMQLPKTLFKIVSNKHECSSENSLETIRKWPHSRHHCGISTKWDGDEEFSHERRQLPNEVERKDVESLQ  
NNSPLSLMKGKNSQNSTAEHETNLNFRAMNKINSITFILCPQFFQVNYLLAFDYFVSHKICYESMYRIL  
SDWLCYCNQRCVDHPVQCWQDIPYIMNFHSPLLAVCGLTNKYSILILQAIRHFA

The following DNA sequence Seq-2511 <SEQ ID NO. 53> was identified in *H. sapiens*:

GAAGTGGGATTCCATCTTCCGCAATGTATGTATTCTGTGATATGATTTTGGTTGAACTTGTGAAGAAAAT  
ATGGAAGGAAGAAGAATTTAATACTCTTCTCAGATAATTGTGGCTATTCTTTTAAACCTCACAAAAGCTTG

ACAAATCGTATTTTCTCAAAGGTCAGTTATAATGTTGAATCTGTAAGTGTACTGATGACCTTCTTCGTACT  
CTGTTATATTAATAATCTCTTGATCTGTGTTACACTTGGATAGAAATTTTTTCGCATCATTTTGTACTAGCT  
TGCATGAGTTATTTGGAACTATTAGCTCACTGACTTGTGCTAATCTTACAAATGTTGACATGTTTCACTA  
TACAATATCAAAATTGCATTTGTCAATATCATCATCACTTAGCCTCTAAGGATTGGGATGCTAATAAGCT  
TACAGTATAAGATGCAACTTTTTTCCCCAACTTGAGTTTGTGCTTGGCAACACATTCTGCCAGTTATTT  
TCCTTGAAGTGACAGGCTAACTTTGTTATTTTCTTAAGAGAATGTGTGCCAAATATCCAAGTCTGAGTAAC  
CATAGTTCGTCTGTCACTGGTTTTTTAAGTGGAATGATGTTCCATTAAAAAAGTGCTAATTCATCTCA  
TAACTCAATCGTGTAACTACTTTTCTGGAAGTGACCATTC

The following amino acid sequence <SEQ ID NO. 181> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 53:

KWDSIFRNVICILYDFGNLRKYGRKKNLILFSDNCGYSFKPHKSLTNRIFSKVSYNVESVTVLMTFFVLCYI  
KISSVLHLDRNFFASFCTSLHELFGNYLTDLCSYKCHVSLYNIKIAFVNIIITLASKDWDANKLTVDATFF  
PKLEFCHWQHILPVIFLEVTLGCLYFLKRMCAKYPSSLNHHSSSVSGFLSGNDVPLKKVANSSHNSIVVLFLE  
VTI

The following DNA sequence Seq-2512 <SEQ ID NO. 54> was identified in *H. sapiens*:

ACCCCTCCCCCAATTCAATTACCTCCCACCATGTCCCTCCCAACACAGTGGGAATTCAAGGTGAGATCTG  
AGTGGGGACAGAGTGAAACCATATTAATTATATAATCATAAGATTGTAACTCTATGAAGCCAAGAAATAT  
GTGTGATTTTGTTCACCATTATATCTCAAGCACTGGCATAGTATCTGGCATGAAATAGATGCTTAATGAA  
CTATTTGTTTAAATGGATGTTGATCATTTGTGTTGGTGACTTTACAAGGTTAACATTTTTTCCATGTTGAG  
GACATGGGCAACTGTCCTATGGCTTGTGGCTGTGATGATGCATGGCAGCACTGGGGTGCTTCCGACTGGT  
CTGCTAAAGACTATTAATAATTTTCTATATCTGCCAATAGGAATCTTATTTATTTTGTCTGTGGCTGTG  
TTTCTGTTCCTTCAGGGCACAGTGAAGCCCCATTTCCTCAAGTTGTTTTTCTAATGATTTTCTTTGCC  
ATATCTGAACCAATTTCTGGTGTATCAAATTTCCACAGAAGACTGTACTCAAGATGGCAGACCAAGCAC  
ACATGCTGATCTACA

The following amino acid sequence <SEQ ID NO. 182> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 54:

PSPQFNYPPLPPSHNTWEFKVRSEWGQSETILIISDCKLYEAKKYVFCSPLYLKHLAYLANRCLMNYLFNG  
CSFVLVTLQGHFFPCGHGQTVLWLVAVMMHGSTGVLP TGLLKTINNFSISANRNLIYFCLWLCLFFRAQS  
PICLKLFFFSFAHILNQFLVYQISTEDCTQDGRPKHTCST

The following DNA sequence Seq-2513 <SEQ ID NO. 55> was identified in *H. sapiens*:

ATAATATACTGAAAATTCAAATTTTGATTACTTTTTTCAGAGTTAAATGGTTAGCAATCAAACAATTGATTA  
GAAGCTTTGTATCAGGTAAAAATAGGATATTTAGTGTAATATGATTTTCTTTACGGTCTTGATACATCTT  
TTCACCTATTTCAACTGAAATATATATGTAAACATAGGGGGTAGGGACCACAATCAACTGCAGAGAATCTT  
CATGTAATCATAAGATCGACTGAGTTAAATAAAAAAATCAAATCTGTGAGCAACACATAATATATGTTT  
AGGATTAGAATAAACTATCTGCATGAAAATGTTTAGAAGAACCTCTATTTCATCCACAATATCTTCTCC  
TTGCCACAAACCAGGGTTTGTGCAAGCCTGGAATTAATGGCATAACCCTTTCTGAGTGCTACTATTCC  
TGAGTGCTACTAGGCCAGGGATTGGCCTAGGTACTGTTGCTCGCAGCACAGAAAGCCAATCACTGAGACA  
AAGAGTAGTGCCAAGGAAGAAGGCTTTAATTTGGTGCTGAAGTCATGGAGACAGGGAGATAAAATCTCAAA  
TCTGTTGCCTCAGTTGACTAACTTAAGGGTTTATACAGCAGGGGAAAATATAAGTATGTGTGAG

The following amino acid sequence <SEQ ID NO. 183> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 55:

HTYLYFPFAVTLKFSQLRQIDFISLSPLQHQIKAFFLGTTLC LSDWLSVLRATVPRPNPWPSSTQEHSGK  
GMPFNFQACTNPGLWTRRRYLWMNRGSSKHFSRFSYNPEHILCVAHRIFFLFNSVDLMITRESAVDCGPY  
PLCLHIYFSKWKDVSRVTKKIIFTLNILFLPDTSFSIVLLTILKSNQNLNFQYI

The following DNA sequence Seq-2514 <SEQ ID NO. 56> was identified in *H. sapiens*:

TTACAAAAGGAAAATATTCATTCTTTTTGTATATTTTATGATGATTAGGGTTTCTAATACAAAGGAAAG  
CATTCTTTGTATTTGAAACCCTATCATTGTGCTTGCTGAATTGAACATTGCTGATAACACCAGAAGACCC  
CTACATTCTCTACTCAATAGGAGAGCTAATGAGGTGGCATGTGATGTAGATCCATAGTATGTAAGAACACA  
GGACACACACACACACACACACACACACACGCTTATTAATAATGTAATGTTAAATAATACATGCAGG

GCATTTACATTGAATGACGGTTTTGTTTACAGCAGATTTGCTGGTTTCTAGAGGGACCAGTTGATCCACTTA  
AACTATTTTACTTCTTGAGTAGCCCTATTTCTGTTTGTCTTTTTTCCCCCAAAAATTTATGGCCAGGAG  
CTACC

The following amino acid sequence <SEQ ID NO. 184> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 56:

LLAINFWGEKGQNRNRATQEVKFKWINWSLLNQICCKQNRHSMMPICIVLFNITLLISRVVCVCVCVSCV  
LTYYGSTSHATSLALLSRECRGLLVLSAMFNSASTMIGFQIQKNAFLCIRNPNNHKNIQKRMNIFLL

The following DNA sequence Seq-2515 <SEQ ID NO. 57> was identified in *H. sapiens*:

TTTAAATGTATGAATACTCTCCTTCACTGGGAGGATCAATTGGATCAGAATCTCCGAAGGGTGATGTTCA  
GGTACCGATACATATTTTAGGAGTGCCTTGATTATATTACATAGCTGGGATTGAGAATTGTTGATGTAGGT  
TATCTGGGCAGCCACCCAACACCATACACCACCACCTGAATGCAGTGCTGCCATTGCATTTATATTTATAC  
TCATATTTGTAACAAATAATCTAGTAACACAATGATATTTAACTTTTCATGTTTCAGTAAGTATAACTGGC  
TATCATTAAAGCTGCTCTGTTCTATTATCAGAACGACAGATTTACAAAGGCAGCCTTTTATTCATGTTGAGT  
TATTTTCCAGTTGTAAAATCACCTCCCACCCTTTTATTGTGCTAGTCATTCAAACTAGAAAAATATTTT  
GGAGGAATAACACTGGAGTTTAACAAATGACTTTTTAAATATTAGACTTGCAATAGCAAAAACAACATAAA  
GTAAATATTATGCATTTTAAATGTTTCTGGCACTAAGAAAGGAACAGAGACAGACATGAAATGAAACGA  
CGAAATTGTGGCAGGTGAAGTTCCAATGACCTTGGAAAATGTTACCAGTAATACTTCACAATATATACCA  
GTGATGGGAAAA

The following amino acid sequence <SEQ ID NO. 185> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 57:

FPSLGIYCEVLLVTFKVIKSPATISSFSFHVCLCSFLSCQKHLKCIIFTLCFCYCKSNFKVICTPVLF  
LQKYFLVLNDHNKRVGGDFTTGKITQHEKAAFVNLSFNRAAPVILTETKVYHCVTRLFVTNMSININAMA  
ALHSGGGVWCWVAAQITYINNSQSLCNIKALLKYVSVPEHHPSEILIQLILPVKESIHTF

The following DNA sequence Seq-2516 <SEQ ID NO. 58> was identified in *H. sapiens*:

ATTGCTTATGAAATGTATTAAGAAAATTGTGTGCTTAACAAAAACAACTTATTCAGGTTTGATGGTTTGC  
TGATCTACACACACACACAAAATGGCCCTTTTACAAAGCAGTTGGCTTTCATCAACTTCTCCATAATG  
CCATACATGCATACAAATCACACTTTCAGTTATTCAGTGTAGAAATCTCATCAATAAGAAATCCCTTGGA  
TAACGGGCCCTTCATTGGCTTTCTTTTATGGCCAAATGCTGAGTATTTTGGCTTGAGATGATAACTTTA  
TTTTAAGCCTGAGAGAGCAGGTGACTTGCCTTGGTCTAATGATACTAAGCAGCTGCCACAGCCTGTTTCA  
CATCCACTGGAGAAGACTGTTCCCTGGAGAGGGAGCATAACTGTGCATGTCTCTTTCAAGATGTCTCTT  
TGGGTACCATGTTGGGAAGTGACTTCCAAGGGTGAGGAGTGCCCTGTGTTTAGCTTTTGGTTACATCCC  
TGTGCACAAAGGAGAGACCGTGTTAAAGAGTTGAGA

The following amino acid sequence <SEQ ID NO. 186> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 58:

CLNVLRKLCAQKQTYSGLMVCSTHTHTKWPFSSQSSWLSSTSPCHTCIQITLSVIHCRNLINKSLVITGPS  
LAFFYWPNAEYFWLEMITLFAESRLALGLMILSSCHSLFHIHWRLFPGEHAHNCACLFQDVSLGTMGLGSD  
FPRVRSALCLAFWLHPCAQRDRVKELR

The following DNA sequence Seq-2517 <SEQ ID NO. 59> was identified in *H. sapiens*:

TTCAAAAGTGATCTCTAAATTTTCAAAGAAAATCAGATATTCAAGGGCTCTGGTAGGAGCCTTTAGTCCTTT  
ACTCAGTTTTTACTGACTATATGAACCTGCACATAATCTGTCTGTAATCCAAATGAAATGGTCTAATGCA  
CAAACATATTGTTTTCAAGAAATACCGAACTTTTCTCTGACTGACTAAAGGTTATTAAAAATGTTTGTTT  
TAAATCATTTCTAATTTTTGATTTAAGATGTCTGGTCTCTCCCTTCCCTTCTTTGATAAATAAGGCTGCT  
ACATTTCTCAATTTTCTAGATGTTTACGCAATATAATAATGATAAAATCTAAATAATGGACGACAAAAA  
TTAATGTTACAAAAGGAAAATATTCATTCTTTTTGTATATTTTATGATGATTAGGGTTTCTAATACAAA  
GGAAAGCATTCTTTTGTATTTGAAACCTATCATTGTGCTTGCTGAATTGAACATTGCTGATAACACCAGA  
AGACCCCTACATTCTCTACTCAATAGGAGAGCTAATGAGGTGGCATGTGATGTAGATCCATAGTATGTAAG  
AACACAGAC  
GCAGGCATTTACATTGAATGACGGTTTTGTTTACAGCAGA

The following amino acid sequence <SEQ ID NO. 187> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 59:

LLTKPSFNVNALHCIIHYIINNPCVVCVCVCVCVLTYYGSTSHATSLALLLSRECRGLLVLSAMFNSAST  
MIGFQIQKNAFLCIRNPNHHKNIQKRMNIFLLHFFVVHYLDFIIIIILRKHLEKLGVAALFIKEGKGETRH  
LKSKIRNDFRTNIFNNLSVREKFWYFLKTIKLCIRPFHLDYRQIMCKFISVKTVDRLLEPLNIFLSKFR  
DHF

The following DNA sequence Seq-2518 <SEQ ID NO. 60> was identified in *H. sapiens*:

CTTGATCACAGGTTATCCTAACAGACACAATAATAATAAAAGGTTAGAAATATTGCAAAAAGTAGCAGAG  
GCATGAAGTAAGCACATGGTGTGGAGAAATGGCTCTAAGAACTAGCTCGATGTAGAGTTGCCGTAGTCC  
TTCAATTTGTAAAATATGCAATGTCTATGAAGCACATAAAGCAAAGTGCAAGTAAACAAAGTACGCCTGT  
AAGTGCTGATATAGTAAGCTTAAATTTTCATTATCACACCCCCTTGCCAGGTTTGTAGTTTTGTCTTTAT  
AATATCGTCTGTATATGAAACAAAGTAAATCTGTTTATTTCTTATAAAGCTTTCCAGAGTATCTAGTA  
TAATTCGTGCATGTAGAAGACTTCTCAGTAATTATCCACTACTCAAGAGACAACCTGCTGTGTGGAGTGA  
CTGAATCCTAGTGAGCCTGCCCCACAGTGGCCGCA

The following amino acid sequence <SEQ ID NO. 188> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 60:

CGHCGAGSLGFSHSTQQVVSVDNYEVFYMHRRIIDLTGLKLYKKNRFYFVSYTDDIIKTKTTLNLRGGDNE  
NLSLLYQHLQAYFVYLHFALLCFIDIAFYTNRTTATLHRASFLEPFLQHHVLTSLCYFLQYFPFYCYVC  
DNLS

The following DNA sequence Seq-2519 <SEQ ID NO. 61> was identified in *H. sapiens*:

CCCGCCTTGGCCTCCCAAAATGCTGGGGATTAGGAGGCGTGAGCCACTGTGCCCCGCCAGGACTCCACCAT  
TTTACAATAAAAAATAACATTACCATATCATCAAATAATATGTGATTATTTGATACTTAAAAATAGTACAG  
TATGCAGATTACTGGAATAGTGAAAATTGATAACGCAATCCCTAGTAGAAAGAAAATCCGAAAGAGTTCTG  
TATACCGGCTTTTCAGTACATTTAAATATATATATGTTTGAACAATTCATCTTTATCCCTAATACAATACT  
TTTCAAAAGCTAATTTATAAATGTCTAGTTTGTACAGATACAACTGTATAATATCCAAATATACAGATAT  
TCTCAGAATATACAGATTAAATATACAGAAATAAATGTATGGTTATTGCCTGATCATAATTCCTTAGGGAA  
GGCAATAATTCACAATTTATGTACCCACAGTGGCAGTGTAGAGAGGTGGTTTTGCCAGTGATTACTTAATA  
CTAAGTTGCCAACACAGTACTTAAACCTTCATTTATGAGAGTCTAAGAGATCTCCTTCCTGGAAATTATC  
AAGTATGCATCGAGGCTACACAATAGAAAGAAATTAGCTTTTAAACAATGATGCAGTCCGGTTGCAGTGG  
CTCACGCCTGTAATCCCAGC

The following amino acid sequence <SEQ ID NO. 189> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 61:

LGLQAATATGLHHCFKSFLSIVPRCILDNFQEGDLLDSHKRFVLCWQLSIKSLAKPPLYTATVGTIVNYCL  
PGIMIRQPIYFCIFNLILRISDYIGYYTVCICTNHLISFKVIVLGIKMNCNIIYIFKCTESRYTELFR  
FELLGIALSIFTIPVICILYFVSNHILFDDMVMLFFIVKWWSPGRAQWLTPPNPQHFGRRR

The following DNA sequence Seq-2520 <SEQ ID NO. 62> was identified in *H. sapiens*:

AACAATCCCAAATAATGTAACAGATATAAAATATTAATGCTAATATTTAATACCCTGATCATAGTAGGTC  
CTAAATAAATGGTACCGAGTGCTCATTGTAATACCTGATGAAGAAAGTAAGTTGCAAAAATAATTGC  
TTTCTATTATGTAGCTATACAGAGATGAGACAGTTCCTACTTCCTTAATTCTTAAAGGAGCAGAAGAGTAT  
GGCACCAGGAATAGAACTTGGGGCACAGCAGGTTCTTTCTACTGCAGAAAAAGGCCATTCTGAAGCCACT  
TATAGTTACTTCTGTCTCCAGAGCCTTTTCTGTGCATATGAGGTCAAGGTCAAGTGTCCATGGAGCCTGGA  
AGGCTGTTCTGAAGAGAAAGGAGAGCCATGGGTTACGCAGGAGCTGGAGTGGACAGCTTGGCGGGGAG  
CTGGGTAGGGTATGATGCTGGGCATGTTCACTGTGGTAGTTAGTTCTGGGGTACAGGCATCCAAAATGCT  
CAGGTGCACATCACAGAAGGGGAAAGGAAAGAAATCTCGGTCATGCTCCTTGGAGTTTCTCAGAGAACA  
AGAATTTACAGCACAGCTGAATTAGGGCAGAGAAAAGACCACCGAGTGCTTGTCCCTTTTGTGGGCTCG  
GGGGAATGC

The following amino acid sequence <SEQ ID NO. 190> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 62:

ISPEPTKRDKHSVVFSSALIQLCCKELFSEETPRSMTEIFFPFPFCDVHLSILDACTPELTSHSEHAQHHT  
LPSSPARTVHSSSCVNPWLSFLFRFAQAPWTLTLTSYAQKRLWETEVTSIGFRMAFFCSRKEPAVPQVLF  
LVFPYSSAPLRIKEVGTVSSLYSYIIESNYFCNLLSSSGYIMNEHSVPFIDLLSGYILAFNILYLLHYLGL

The following DNA sequence Seq-2521 <SEQ ID NO. 63> was identified in *H. sapiens*:

TAAATTACAGTCTGTAAATAAGAGGTAGACCATAATTGCCATTCCTTAGGTATAGACTATCCATAGTGATT  
GTCTTTCCAGACAATGTGGTATAGAAAGGAAGAACAAAAGAGAAGAAATTCATAGTGAAACAACCTGATAA  
ATAACTTCTCAAGCCAGCTGACCAAGGTTAACATTAACAGTGATTAGTTATATTGACTGCATGCACTTTTA  
TAGGAGGCGATATAACAGCACTTCCTCATCTCTACTGTCTTCTCCCAAAAAACCTTACCCAGGCTAAT  
CATGAGAAAACCATGAGACAAAAATACCAACTAAAAGCCATTCTATAAAATACTTGTCCAGTAATCCTCAA  
AAATGTCAAGGTCTTCAAAAATAAGGGAAGCGTGAGAACTGTCACTAACTAATAGGAGCCTCAGAAGATAC  
AACTACTAAATGTAATGTATTCTAGAGGAGCTTTTGACATGTAAATGAACATTAGGGAAAACCTGGGGAA  
TTACAAATAAACTATGGACTTAAGTTGACAATAATGTATCAAGATCAGTTTTATTAAATTGTGATCAGTGTA  
CCAGGATAAAGTTTTTAAAAATAGATCAGGGCACATTGGTTCATGGCTATAATCTCAGCTCCTTAGGAGGCT  
GAGGAGAGAGGAGT

The following amino acid sequence <SEQ ID NO. 191> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 63:

LLSPQPPKELRLPTNVPSIFKTLWYTDHNNSYIIVNLSPFICNSPGFPCSFYMSKAPLEYITFSSCIFGS  
YLQFLTLPLFLKTLTLFLRITGQVFYRMAFSWYFCLMVFSLAWGKVFWEEDSRDEEVLFISPPIKVHAVNIT  
NHCCPWSAGLRSYLSGCFMTNFFSFVLPFYTTLSGKTIITMDSLRLRNGNYGLPLIYRLF

The following DNA sequence Seq-2522 <SEQ ID NO. 64> was identified in *H. sapiens*:

TCAGCCTCCTAAACACTTTTGTACTGTACACCCCTCAACCCCTGCCAACTCAAGGAATTATAAACTCACA  
AATAGCTCCATCAGCTTCTGCCTTTAAGGTTTCAAGTATTAGTTTCTAGGGTTGCCAACAAATTAACATAAA  
CTTGTTAGCCTAAACAAACAGAAATTTACTCTCTCATAGTTTGGAGACCAAAATCAAGGTGGTGGCAGGGC  
TGCATCCTCTCCAAAGGCTCCATTCTTGCTTCTTTCAGCTTCTGATGGCTCCACATATCCCTTGGCTTGT  
GGCTACATCACTTTTATATCTACCTTGGTGGTCTCATGGCTTCTGCTCTTCTAGGTGTGACTCTTCTCTG  
TGTCTTTCTTTTATAAAGACATTTGTCATTGGATTAGAGCCACCTAGAAAATTTAGGATAATCCTACCC  
TAAGATTCTTAACACTTACAACCTTAATTTGAGGGTCTGCCAAGCCTTTTTTTTTTCCATATAAC  
ATTTACAGGTTCTGGTAATTTGGACATGGACATTTTTTGGGTGGAGAAAGGTACCATTTAACCAATACAG  
CCTGTT

The following amino acid sequence <SEQ ID NO. 192> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 64:

SASTLLYCTPLNPCQTQGIINSQIAPSASAFKVQYFSRVANKLTTCPKTTEIYSLIVWRPKSRWWQGCILS  
KGSIPCFQLLMAPHIPWLVATSLSYLPWWSHGLLLFVLFVSFFYKDICHWISPPRKFRILPDSHLQPF  
EGLPSLFFFPYKITFTGSGNLDMDIFWVEKGTIPNTAC

The following DNA sequence Seq-2523 <SEQ ID NO. 65> was identified in *H. sapiens*:

ATCCATTTAATGAAATGTCTATTATTTACCTGAATATAAGTTTAGATTCTAAATTATGACAAGTTTATCTA  
CAAGTACTTATTTTATTACATTTCCATAATTATTTTATTTTAAATAGTTTACCTAGATTATTTACGAAACCT  
GCAATAGTTATCATTTAATGTTACTTTCCTGTCAACATTTTATAGCTTGTGGATTTCAGGTGTTACCTAC  
AAGTGAGAACCTTAAGTTTAGATACATGATTATTTTACAAAATAATTCAAGTTTGTAGCTATTTTCATTAA  
CCAATATTAATGTCTTATTTATCAAAAATTACACAAGCAAAGGTCATTTCTGTTTTGGTCTGGGTTTATAT  
TTTAATAACTCTTATTTCAAATTTGACCCCTTATAGTATTTTGGTAGAGATACGTATTGAAGTCTCTTGA  
CTCCAGAAAAGGGAGTTTTACAGAGAAACAACTTTGGATGTCACTAAATTGGGGAGATTAAAGATTCTC  
TAGAGAAAGCGGGGGGCTCCAAAGCTTCAGCAATTTGTCCTATTGATTGAGCCATAAAGA

The following amino acid sequence <SEQ ID NO. 193> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 65:

PFNEMSIYYLNLISLDSKLQVYLQVLISLHFHNYFILIVLYLDYLRNLQLSFNVTFLSTILLVDFRCLPVRTL  
SLDTLFYKIIQVLAIFIKPILMSYLSKITOAKVISVLVWVYILITLISNFDPLYFGRDYSLLTPEKGVLO  
RNKLWMSTKLGRLLKILRKGAPKLQFVLLIAIK

The following DNA sequence Seq-2524 <SEQ ID NO. 66> was identified in *H. sapiens*:

TCTTATGTCTTTTGTGACGCTTCATTGAACTGTGGTAAGCTAATTTGTTAACTTGCAAATAGTGTAACCC  
TTACACTCTTTACAGCTCTTGACAATACTATATTTTCAACAACAAATGATCTAATGAGAAAAGCGGCAT  
TAACATTTTCTTGCAAATCTCCAATGTCTAGCTTAGTAGTAGAGAGCTGAGTTCTCGCATCTGATACATTC  
TATTCTTGCAATATGTTGTTTTGGTTGAAATATGTGACAAAAATCTGGTCTCACACAGACATAT

The following amino acid sequence <SEQ ID NO. 194> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 66:

SYVFCQPSLNCGLICLANSVKPYTLYSSQLYFQQQNDLMRKAALTFSCSPMSSLVSVLASDTFYSCN  
MLFWLK YVTKIWSHTDI

The following DNA sequence Seq-2525 <SEQ ID NO. 67> was identified in *H. sapiens*:

TCGTCAGCTCTGCGCTCACCTGCTCTCTCCCTGGTCTGTCACACCAAACCTGTTCTGCTCAAAGCTTTG  
CCCTGGGAGTATTCTTCCCCCTTGCAAAGCTGGGTCTTGCAAAGCTGGGTCTTCCCATCATTCAAGTTCAA  
AATCACCTCCTGGGATAGATCTTCCCAGACCAACCAATGTGGAGTACCTTTCTGACCGGAGATGTTCCA  
CCATTACATCACTATGTTGTATTTTACTTACACATCATCTCAAATTATCTGTGTATTCACTAATTT  
GTTTCTTTTCTGACCTGCCCCGTGCCACGCTGAGTGTTCATGTGGCGCCCGGCTTGAGTGTACTTTCA  
CTAGCACAGCACCCATTTCTCTCTTGTGAATTGCTGAGACTCTAGTGCCCATTTCAAGACTCTGTCTTCAG  
ACTTAAGGATAAGAGGAATAGACACTAGGGTGGGGGAATGTATAGGCTATTAATATGAGATGAAAATGAA  
AAGATTGCCAGGTAACACTGCAGTACAGTTGAAGTTAGATAGCACGAACCTCTGTATTTTCCAAGACTTTCT  
CCACCTACTCTTGACAGCCTGGGTGAGAATAGAAAGGTTGACAACAGAGACAACATAAATTTTGGGCAGAG

The following amino acid sequence <SEQ ID NO. 195> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 67:

VSSALTCSLPGPAHQTCCLKALPWEYSSPLQSWVLQSWVLPPIIQFKITSWDRSSQTNQCGVPFLHRRCS  
ITSLCCILLTHSSQIILCIHFVSFLHLPRATLSVHVAPGLECYFHHSTHFSLVNCDSSAHFRTLSSDLRIR  
GIDTRVGGMYRLLIDENEKIARHCSTVEVRHELICIFQDFLHLLLTAWVRIERLTETITLGR

The following DNA sequence Seq-2526 <SEQ ID NO. 68> was identified in *H. sapiens*:

ATGCTGTCTTGATGAAGTTGGGAGGGACAGTTACCTAATGCTACCACTCTTGAGTTGTTCTGGAACAAAT  
CACAGTGGAGTCTGAGATGGGAGTGAAACTAAATGATATCTGCAGCCTATGCAGCTGCCAGCCCTGTCCA  
CTGGAGGCACCCACTTTATTCTTACTGAAATTGCCATCTGTTCAAATCCTCCGATCATTATCAATGATCTC  
CTTTCCCATCTAAATTGTTGATTACTGTTAATTGAATCTTGGGACTATCTTTCAGTGCATGATTGAATCTC  
ATTTAGGGAAGATTTATAGTCACTGGTACTTGAAGGAGAGGCACAGTTATAGTGGTTCCTTGGTATACATA  
GGGAAGTGGTTCAGGACCCCTTTGAGAATACAAAAATCCAAGCATATTCAAGCAGTCCCAAGTTGGCCCT  
GTGGAAGTCACTGTAAAGAAAAGTGGGCCTTCCATATTTGCAGGTTTTGTATTCTGTGAGTACTCTACTTT  
TGATCTGCATTTGGTTGAAAAAATCTGTGTATAAATGGACCCATGCAGTTCAAATCCATGTTGTTCAAGG  
GTCAATTGTATAGCTTT

The following amino acid sequence <SEQ ID NO. 196> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 68:

CCLDEVGRDSYLMPLLSCSWNKSQWSLRWEKLNDCISLSCSQPCPLEAPTFLFLKLPSVQILRSLSMISF  
PIIVDYCLNLGTIFQCMIESHLGKIYSHWYLKERHSYSGSLVYIGNWFQDPLRIQKSKHIQAVPKLALWNS  
PVRKVGLPYLQVLYSVSTLLLCIWLKKICVMDPCSSNPCCSRVNCA

The following DNA sequence Seq-2527 <SEQ ID NO. 69> was identified in *H. sapiens*:

AAGAAATTTTCACTTCTGCCCCACCACAAAAGAGACAATAGTTTGAATCTGAATTCAGCCAAAGTTAACCC  
CTTGCTTAAAAAAGAAAGGAAAAGAAAAGAGGAGAGGGGAGGGGAGGGGAGAGCCAAAATTCAGCCA  
AAATTAACCTCCTTGCTTAAAAAAGAAAAAAGGAGAAAAGAAAAGGCCAAATCAACAACACGTTCAAA  
GATAACAGAATCCAGTCTCCACACTATATCATTTGTTGAGAATATAATTCAAATTTATCAACATATGAAAA  
AACAAGAAAAATCTAACCCATATTCAAGAGAAAACACAACCAATGGAGAAAAATCCAGATTTTTTTTAGTA  
GCAAAAATCTGTAAGCAATTATTGTAAGCAGCTTAAGGACATAAAGGAAAATGTGCTCACAAATGAATAAAC  
AAATACAAAATGACAGCTGAGAAATGGAATAAAAAAGGTCCAATGGAAATTATGGAAGTGAATATGACAT

TATTGGAAATAAAATATACACTTTCCAGTTATTTAAATCTTCTTTTAAATCTGCCTTCTTTATGTCCAC  
ACCATAGTAGTGTTCACTAAATTCTTTTCTATAAAGATGGGATCTCACTGTGTTG

The following amino acid sequence <SEQ ID NO. 197> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 69:

QHSEIPSLKRITLLWCGHKRRQILKEDLNNWKVYILFPIMSFVFPPLDLFYFHFSAVILYLFIHCEHIFL  
YVLKLLTIIAYRFLLLKKIWIIFLHWLCLLNMGIFLVFSYVEFIIFTMICGDWILLSLNVLLIWPFLFSFF  
FSFLSKELILAEFWSPLPSPPLSSFLFLSFLSKGLTLAEFRFQTIVSFVVGSRNF

The following DNA sequence Seq-2528 SEQ ID NO. 70> was identified in *H. sapiens*:

TTTTTTTCTCTATTTCCCTCAATTACTACTTTCTTTGTTTTAGTTCATTTTTTATAGTGACACATTTTG  
ATTACCTTTTTATTTCTTTTGTGTACATTTTGTGGATATTTTCTTTGTGGTTACCATGGAGGTTACATGT  
GACAGTACAAAGTTATAACAATCTATTTTGAATTAATACCAACTTGACTTCAATTGCACCCAACACTTTGC  
TTTTTTACAACTTTCCCTTCTGCTTTGTTATGTTATTTCTGTCAAAAATCAATCTTTATATATGTTGTGT  
ACCTATTAACATGGATTTATAATTATTTTTGTGAATTTGCCTTTTAAATCTTTAAAAAATAAAGTGTAGT  
TACAAGCCAAAATTATATAAACTATTAGTTTTATAATGTCCATGTATTTGCCTTTACCGGAGATCTTTA  
TATTTTCTTAGTGTTCAGTTACTGTCTATTGTCTATTTTATTTCAACTTTGAAGGGCTGTCTTAACACTG  
ATTATAGTGGAGGACTAGTAGTAATGTAGCCTCTTAGCTTGTTTACCTGGGGGTGCATTTATTTTTGCCTA  
ATTTTAACAGGACAGTTTGTCTAAATACAGAATTCTCAGTTGACAAGTATTTTCTTTTCTTTTAGCACC  
TTAAATATATCATCTCTGTGCCTTCTGGCCTG

The following amino acid sequence <SEQ ID NO. 198> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 70:

FFSHFLNYYFPLEFLVHFLHILITFLFPFVYILWIFSLWLPWRLHVTQSYNNLFINTNLTSIAPNTLLFYN  
FPFLLCYVISVKNQSLYMLCTYHGFIIIFVNLFPKFFKKSUVVTSQNYIKLLVFIMSMYLPPLPEIFIFS YV  
KLLSIVILFQLRAVLTLIIVEDCSLLACLPGGAFIFAFQDSFAKYRILSQVFFFFFHLKYIISVPSGL

The following DNA sequence Seq-2529 <SEQ ID NO. 71> was identified in *H. sapiens*:

TTCTTATCTCTAAAAATGAGAATGATGCTGGCTCTCCCACTCTCATAGGGCTGTTATAAAAAACCAATGAGG  
ATTGTGCTTTTGGAAAATGCTTGCAAAAGATCAAGTGCTACATGTGTGTAAATAATTTCCAGGAATATCC  
CCAAAGTTTTTGGGCTGGTATATCATATAATTTCTTTTTCAGTAATTGTGTGGAAAAATACTTTATAAATGCA  
TAGATATAGATAGATATTTTCATATAATACATGCAGTGATGATCTGATGAGAAAAATGATGTACCCTGAAT  
GTTTTATCTTTAATAGCACTGGCAATCTTGATATGCATGAATCTTTTAAACCATGCTACAAACCTCTGT  
TTCATTTAGAAATATTATGTCTTTTTTGACTTACCCCAAAACCCCAAAATGACCAATGGGAATGAAATATGC  
CAGCATGCACCTCATGCCTGGGAAGATACATAAAACAATGGGTTGAGGATTGGATTAAAGAAAGACAAAAG  
GCCTTCACACAAAGTGATTCTTCTTAAATTTGAAAGGTTACCAGCTAACAAAGATAGGAAGGTAGTCTCTTTG  
ACCTTCTGCTATTTCAGAGAGATATTGGCAATAAACAATTATATGTGTGTGTAGTGTGTGTGTGTGTGT

The following amino acid sequence <SEQ ID NO. 199> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 71:

LISKMRMLALPLSGCYKNQMRIVLWKMLAKDQVLHVCKIIFQEYPQSFWAGISYNNFQLCGKILYKCIDI  
DRYFHIIHAVMIEKCTLNVLFSFNSTGNLDMHESFKTMLQTSVSFRILCLFLTPNPKMTKWENMPACTSCLG  
RYIKQWVEDWIKERQKAFTQVILPKIERLPANKIGRSLPSAIQRDIGNKQLYVCVVCVCV

The following DNA sequence Seq-2530 <SEQ ID NO. 72> was identified in *H. sapiens*:

CATTTGATTGTGATATGGCTTTTTTGTCTTAACACCATAACCCAGGGCCCCGACATAAAATTAATGAATTAGT  
TAAGCCTGTTAAGTCCTCTGTGCATCCTTCTCTCTATTATATTAACCCCTCCTCACCCTTAGACTTTTAT  
TGCTCAGTGCATATTAATAATCTTCTGATTAGGTTCTAAACACAATTACATCCCACACTTTAGTGCAGATA  
TCTTTCCATGTTCTTCAGTTTGTTCACAGCAAATTTCTAGATTCTCCACATAGATCTTACATTTTTTC  
CCCACCTATTAACCAAACTGCATGACTCACAGCCCCAAACATCCOCTAACTATTACATTAGATAAACCACC  
TCTCTCAGTTTCAACTGCCTATGTGTTTCTCTGCCCCACTAGAATTATACCAAGTATTAAATCAGCGTAAA  
TTGTCACCTTTTTTCAGGTAACCTTTCTTATTCTTGTCTACCTGAAAATGCAGTTCTTTTCACTCTGCTTCT  
TGGCACTACAACCACACCTCTTTTATGGCATGCATTATATTGAGTTTGTATACCTCTGCAATACTTACT  
TCAGCTCAAATCTGTTTGAAGTCACGAATTCGGCTAGTATTTACCTCTGTGTCAATGGCATCCTGCTGGA  
AAGTAGATGCAGGCTTGGG



The following amino acid sequence <SEQ ID NO. 200> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 72:

ILYGFFAHNNPRARHKLMNLSLLSPLCILPPIILTPSSPLDFYCSVHIKIFLGSKTQLHPTLCRYLSMEFFS  
LFPTANFILHIDLTFPPHSLTKLHDSQPQTSPNYYIRPPSLSFNCLCVSLPTRIIPSIKISVNCHEFFQVTE  
LFLFYLKMQFFHSASLALQPHLFYGMHYIEFVILLOILTSAQILFEVTNSASIYLCVNGILLESRCRLG

The following DNA sequence Seq-2531 <SEQ ID NO. 73> was identified in *H. sapiens*:

ACCTCCCCCTCCCCCAACCAACTGAGAAGCTGCTCCCTCCCCCAGCAAGCCCAGCGCCAGGTGCTCTTGCC  
TTTTCCCACTGAGAGAAGGCTGCTCTTTGTACTGCCCCCGCTCATTAAACAGCCTCCCCAGCCCTGAG  
TGCCTGATGTCCGCAGCGCTGCCCTACTGTGTGTCAGTGTGTGTGGGAGTGCCAGGCACAGCACCATCCCCC  
AGTTTGGGCGGACTGGGGAGGGCCTGGGGCCCCGCCAGGAGACACCTGTGGGAGGCCTGAGAGATGGCTGTA  
CCTTGGAGATGGCCTGGTGGAGGACAGACCCCAACAGCCAGCTAGGAGGGGATCTGGGGTCTGTCTCTGGG  
GAGGGAAGAGCAGACTCCACGATATCCTTGGGGTCTCCAGATAGCCCACC

The following amino acid sequence <SEQ ID NO. 201> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 73:

TSPSPNQLRSCSLPQQAQRQVLLPFPTEERRLLFCTAPRSLNSLPQPVHCPQRCPTVSVCVGVPGTAPSPSL  
GRLGRAWGPPGDTGRPERWLYLGDGLVEDRPHQPARRGSGVLFWGGKSRLHLDILGVSRT

The following DNA sequence Seq-2532 <SEQ ID NO. 74> was identified in *H. sapiens*:

AGTAGACAAATTTATAAAATTATTTAGAGCAATGAATAAAATAAATAGTATTACTTTTATATTATGTCCT  
CAGTTTTTTCAAGTCAATTATTTATAGCATTGACTATTATTTTGTAAAGCCATAAAATATGCTATGAGTC  
CATGTACAGAATATTATCAGACTGGTTGTGTTATTGCAATCAGAGATGTGTAGACCATCCCGTGCAGTGT  
GGCAGGACATCCCGTACATCATGAATTTCCACTCCCCTCTGCTTGTGTGTGTGGGTTAACTAATAAATAC  
TCCATCTTAATCTTGCAAGCCATTGATAAAGGCATTTTGCAGAAATGCATCTGTCAATTCTTTCCAAAAT  
CCTCTAATTCTTCCTTGAAAGTGACCACTAAAAATTTCCGAAGATTACTAAAATGAAGTTGATTGTATTG  
TCTTGCCAAAATAATTGTGTCTATCATGTTTACTTAAGCAAATTACAGAGAAAAATGAAGCGTATATTAA  
TGAAAGAAGTTTTCAGAAATCAGATTGTCCAAGAAAGGTGACTTTGTTTCTTTCAATTATCTTAAAAATCCA  
ATCCTGAATTTCTAGTAAATTAATTTAATTGATGTTTGATTCAAGCTTTTAAGACTAATAATTATATAC  
AGCTTTCTGAATTAGATAGTA

The following amino acid sequence <SEQ ID NO. 202> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 74:

TNLNYFRAMNKINSITFILCPQFFQVNYLLAFDYFVSHKICYESMYRILSDWLICYCNQRCVDHPVQCWQD  
IPYIMNFHSPLLAVCGLTNKYSILILQAIRHFAECHLSILSKILFFLES DHKFRKITMKMLIVFVLPKLCL  
SCLLKQITEKNEAYIKKFQONQICPRKVTFLFSIILKIQSISSKLILIDVFKLLRLNNYIQLSELD

The following DNA sequence Seq-2533 <SEQ ID NO. 75> was identified in *H. sapiens*:

ATATGAGAGAATACAATATCAATGTTACAGTACACACAGATAGTGAAGTAATGTAAATAGCATTGTCGGG  
AAAAGCCAGAAGCCAAAATTTGTTATATAGATAGAGAAATATTATGCAAAATCCTGGAAATATCTGACAGA  
TGCCCTGCTTGAAGGATAAGCTTATTAGAAAATAAATTACAACACTACTAAAGAACAACAATGTTTCTTGGT  
TTTGGATAGTAGGATTGGTACAGAGAGGTCAATGAAGTGTGTGGTGGCACAGATGGTCTAAGACCTACC  
CTGGCTCCT

The following amino acid sequence <SEQ ID NO. 203> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 75:

EPGVLDHLCHHTVHPLCTNPYPYPTKKHLLFFSSCNLFNKLILQAGHLSISRICIIFFLYLYNKILASGF  
SRQCYLHYFTICVYCEHYCILSY

The following DNA sequence Seq-2534 <SEQ ID NO. 76> was identified in *H. sapiens*:

ACAGTGCCAAAATAATCATCTTTGACAAGCCTTGCTCTGTCTAGTCTTTAGGCAAATTAGCAAATTCAAATAGA

TGGCAACTGCGCCTTGTCCTTCCAGCTATGGTGATTCTCAGGCTCAGTGTGATACTTTAACTGCTTGCCT  
GATCAAAATGCGTGAAAGCTATGTCCATGTCTCTAGAGTATCATTAAAAGGAAATGGAAGCTTATCCACTG  
GTGCGTGCCAAATCTTCCCATCACATGCTATGTTTGATTGACATGTGACACTCTCCTTCATAGTACGTGGG  
GAGCCCAGAACTAGCCTGTGGTCCTTAAAGGAAATGTAAAGAGCCCAAGTCATTTAAAAAGAAGTTATTT  
TTCTAAAGGAAAGAGCCTGCTATTTGCTCAGCTCTCTCACCTTATGATCCTGAAATACTTTGTGTTAGATA  
GCTTCCGAAACTTTTGAGTTACTGTTGGAGAAATAGCAACCTATGTTTCCTCTGTGTTAGA

The following amino acid sequence <SEQ ID NO. 204> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 76:

SAKSSSLTSLALSVLGLKLANSNRWQLRLVFPAMVILRLSVILLTACLIKMPESYVHVSRLKNGSLSTGA  
CQSPFPHAMFDHVTLSFIVRGEPRISLWSLKEMRAQVILKRSYFSKGSLLFAHSSHLMILKYFVLDSFRN  
FVTVGEIATYVSSVL

The following DNA sequence Seq-2535 <SEQ ID NO. 77> was identified in *H. sapiens*:

TTCCTCTTTTGTCTTGGGTAAGAATAGCTTTTGAGATAAGAATACATTTATTTTATTACCTTTGTTGATT  
CCATCATTTTGTATTAGCTTATTGTGTACTTTTATCATATAAGACTTTGGGGAGAGCTTTGCAGCTTCT  
GTTAAATCATGAACTAGTTTAAATTAAGCTCAGTCCAAATACAATTTCTCAAAATAGAGATGTTTCTAC  
CAACATATCATTTTATTTCTTGTGTGTAGTCAAAATAAAAAGATTAGACAAATTTGATATAACAGTCATG  
ATCACAGGTAAACATTAGAAAGGAATAAATTTGCTTTTTCACTTGAAAATCCAAGTGTTTCTTCACATG  
AATTGTAAGAAGATAAACTATACTGACTTAAGGAGGGGAGGCTAATGAGAATTTTTTAGCCCATACATGGG  
CCTCCTTTAAACTATTTTACTTTTAGTTGTCTTACATTATAGAAAGCTACCAGAAGATTTAGTTTATGCAT  
ATACAATTAATAATACAAATACAAATATATGTATGTCTGTCTCTACATAGACCTACATTTATTAGTCAAA  
CAATAAAAGAAAATTTGTTCCAGTTATAAATGCTCAAGCCAAATTTGTCACACAGTCAAGGGCTTACTTT  
GTTCTTTGAATCATC

The following amino acid sequence <SEQ ID NO. 205> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 77:

PLLSWVRIAFEIRIHLFLLPLLIPSFVSVIVYFLSKTLGRALQLLLNHETSFNLSVQIQFLKIEMFLPT  
YHEFYLCVVKIKRLDKFDITVMITGKHKGINFASFLENPSVFFTIIVRRNYTDLRREANENFLAHTWASFKL  
FYFLSYIIESYQKIFMHIQLKYKYKMYVCVSTTYIYSNNKRKFVPIKCSSQICHTVKGLLCSLNH

The following DNA sequence Seq-2536 <SEQ ID NO. 78> was identified in *H. sapiens*:

GTGCTGAATTTGTTCTAATATTATTGGTTACTTGTATTCTACTGTGATGTGTCTCTTCATACCCTCTGACA  
TTTTTCTGTAATACTTTTGGTCTTTTCTTATTGATCTGTAGTCTTGAATTAAGGGTCTCGATAATTTT  
ATCTGCTGTATGCGTTATAAATAGGTTTTTTCACATTGCTGTTTGCCATTCAATTTGATCTTTAGGATTTT  
TTAAGTATTCGGAAGCCCTTTGCAGTCAAATGTTTAATTCTCCCTTTTGGTTTTGCTGTGAACAAACATC  
ACACTTAAAGTCCCTTTCCCTTTTCTGAGTTATACATATATGCCTGTATTTCTTCTAGGACTTTTCTTTC  
ACTTTAAACCTTATTTGATTTGGGATTACTTTTGTGTGTGGTGAAAGGCAGGACCCTGATCTGATTCTT  
TTTCAAGGGGTTTCTGTTTGTCCCAAGATCATTTCTTAAACAGTCCCGATCCTTTGCTTGATTCTCATCT  
GGCGTACCTCATCTGTACGCTGCCTGCCAATATT

The following amino acid sequence <SEQ ID NO. 206> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 78:

VLNLFYYWLLVFYCDVSLHTLHFFCNTFGLFLIDLFLNGSRFYLLYALIGFSHCCLPFNLILWIFLSIRKP  
FAVKCLILPFGFCCEQTSHLKVLSLSVIHICLYFLLGLFFHFKTLFDLGLLFVCGERQDPDLILFQGVSC  
SQDHFLNSPDPLLDLHAYLICTLPANI

The following DNA sequence Seq-2537 <SEQ ID NO. 79> was identified in *H. sapiens*:

ACCTATCATGAAAAACAAATATCCCACGATAAAAACTAGGAACAAGCTCTGTGTAAAAATGTTTTGTGAT  
GCGTGTATTCATCTCACAGACTTAAACCTTTTCTTGAAGTCTAGCATGCTAAAAACACTCTTTTGTAGAAT  
CTACAAAGGGACATTTTGGAGTGCATTAAGGCTATAACGAAAAACCTAATATCCTGTGTATAAAACGAGA  
AACAAAGCTCTCAGTGAAAATGCTTTGTGATGTATCAATTTATCTCTAAATGTTACGCCTTTTTTTTGATTC  
AGCAGCTTAGAAACGCTTTGTGTAGAATCTACAAAAAGACGTTTCAGAGCCCATTTGTCGCTATAGTGA  
AACTGAATACCCAGGATTAAATTAAGAAAAATATTATCTGTGAAAACACTTTGTGATACATGGATTATC  
TCACAGAGTTAAACTTTGTTTTGACACAGCAGGTTGGAACCTCTTTTGTAGAATCTACAAATGGGCA

TTTCAGAACACATTGAGGCCTATAGTAAAAACAAAATATCCCAATGAAACTAGGAAACAAGCTATCT  
GTGAAAATGCTTTGTGATGTGTGGATTCTCTCAGTGAGTTAAACCTCTGTATAATTACAG

The following amino acid sequence <SEQ ID NO. 207> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 79:

LNYNRGLTHDESTHHKAFFSQIACFLVFIVGYFVFYRPQCVLKCPFVDSTKRGFPTCCVKTKFLCEINPCI  
TKCFHRYFSNFPNGVFSFSLATMGSETSFCRFYTKRFAAESKKRRNIRIDTSQSIFTESLFLVFITGYVFR  
YRPCTPKCPFVDSTKRVFLACVKEKVCEMNTRITKHFYTELVPFSFYRGIFCF

The following DNA sequence Seq-2538 <SEQ ID NO. 80> was identified in *H. sapiens*:

ACATTGGGTCAGGATCTTTCTGATGTGTCAATTCTGTCTCAGACTGGTTTCTTCCATAAGATGTGCACT  
AGCAGTGACTTGGGCAGCATACTTTTCATGTTCTATCTTGCATGAGATAAAAAGACAGAGGATCAGAGAAA  
GAAACACAGAGAATCTCTCCCATCACAATGAAACAGAAGTTCCTCTGGAACCTCTTAGGTCAGTTTAGCTG  
AAGAGCCCACCAAGTCTTGATTACCATAATCCTGAACCATTAACCAATCTCTAGCCAAAAGATGGTAG  
TACTATCAGCCTTCCATGGGTTTCCAGCATCCATGGATTCAACCAACCAGGGATCAAAAATATTAGGAAAAG  
AAGTGTGTCTATACTGAACATGTACAGGCTTTTTTTTTTTTCTTGATTCCCGAGACAATACAGTATAATA  
ACTACTTACATAACATTACATTGTATTAGGTGTTGTAAGTAATCTGGAGGTGATTTAAAGTGACAGATG  
TTTGGGGGTTATATACAAATACTATGCCAT

The following amino acid sequence <SEQ ID NO. 208> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 80:

IGSGSFCVNSVLRVLFVFFHKMCTSSDLGSILSCSYLADKKTEDQKKHRESLPSONRSSSGTSVSLAEPTK  
SLPSTIKTNLPKRWYQPSMGASMDSTNQSGKIFRKRVSILNMYRLFFFLIPETIQYNNYLHNIYIVL  
GVVSNLEVISVQMFGGYIQILCH

The following DNA sequence Seq-2539 <SEQ ID NO. 81> was identified in *H. sapiens*:

AGGTGAGCACCAAGTTCTTACACGTGGGAGCAGGATTTGCCTCACATCTGTGCAGGGAGAGCAATTCTTGT  
TAACCACCTTAGGGTTAACCTTCTTCTACTCCTTCCATTAACTCAGCTTAGGTCATTATCTCTATGTATTA  
AGAATCTGTGCACATGATACACACACTTCACAGGTGTTACATAAAAGAAAACAGAGACTTAGTCTCAACT  
CATCACATATTTATTAATTCATGCAGCAAATATTTATTGAAGTCTAATATGTACTAGACACCAGGCCATGT  
GCTGGGGATATTATGCTAAACAGGACAGACACAGAAAAACAGTTAACAAGGGGGAGGGAGTCAAACCTCAA  
CCAGTAAATAGATAAGGAAAATAATTACAAATGTTGATAATATCAACAAACAAAGTAAGATGCTGAGCTA  
GAAACAATAGAGAGAGGAACAATGGTTTGGGGTAGAAACATCAGGAAAGCTTATCTATGGAGGTGACATT  
TTAGGTCATGTGTTAGCT

The following amino acid sequence <SEQ ID NO. 209> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 81:

ANTPKMSPPISFPDVPSTPNHCSSLYCFLAQHLTLFVDIINICNYFPYLF~~TGFEFDS~~LPVNCFSVSVLFSI  
ISPAGHLVSSTYTSINICCMNICDGVETKSLFSFMHLSVCIMCTDSYIEIMTAELMEGVEEGPGGQELLSL  
HRCEANPAPTCKNLVLT

The following DNA sequence Seq-2540 <SEQ ID NO. 82> was identified in *H. sapiens*:

GCCTAGGGCGCCCAACTCAGCTCTCTGCAAGGGGAGTCCAGTGACAGAAACGAATAAAGCCATTTTGCTTT  
CATTGCTCAACCCAGCACGTTGAGGTGTCCCCAGAACCCAGTGACATGGCAAAGATGTGAGGAAAAATG  
ACGTTAGGGTATTGTACCATGTAGTGGGGGAAATTCAACACTGGATGAAGGACTCATCCAATGTGCGTGG  
TTAGGTTTAAAGCCGGGTCTCTGATGTTTACAGGAGGTAAAGCAGAGCCGCTGGAAGACTTCTCTGACCAG  
CAAGGAAGCCATGTGGAAGTACAGGAGGACCCCTGGGAGTTTGGGGAACAAAGGAGGCCGGGAGGGCCCTG  
GTGGACCCAATGACCCCTCAGGGCTCGGGACCGCTAGGCCCGAGGGGTGGGGTCACCCCTACCTTTCTTTAT  
GGCTGTGGTGTCTCCTCCATGGAAACCCAGCTCTGACCACAGGGTGAATGCCT

The following amino acid sequence <SEQ ID NO. 210> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 82:

GIHPVVRAGVSMEEHSHKERGDPTPRARSRALRGHWVHQALPASFCSPNSQGPVLTWLPWCSEKSSSG  
SALPPVNIRPGLNLTTHIGVLHPVLNFPHYMVTIPRHFSSHLCHVHWGSGDTSTCWVEQKQNGFIRFCHWT  
PLAESVGRPR

The following DNA sequence Seq-2541 <SEQ ID NO. 83> was identified in *H. sapiens*:

TATTATGGACCTGGGGAGGGGCCAGGCCTGGGGCAGGGGGCTTTCTCTGATTATGGCGGCTGACGTAGCCC  
ACCCCACTGTGATGTTCCCACTAGCATGGAAGTCCCGAGTCCCTTCCTTCTCCGCTGGCCAGGTGTGGCT  
TCTGGGCAGGCTCCGACCTCTGCGTGCCCTTGGTCTGGAAGCCAGCCCGGGAGCAAGCGGTGAGGTTTGGC  
CAGCCCCGTCCTGGGCGCGGAGGTACCTGCCAGACTGACCTAGTAAAGGGGCCAGGCCGAGGAACCTCCC  
TCCCTCGCTCCCTTCTGTCTTTGCCTTCTGCCGCTCTCCCTCGTCCCTTTTCTCCGCTTTTCCGCGCTC  
CATCTTGCCCTCCTCCCTCCTTGCCTCCGCTCCTACTCTCCCTTCTTCCCTCTCTCCCTACCCCTCC  
CTTTCTGGGGCAGGCGTTTCTCCGAGGCGCACTGAGGCTCCGGGGCGAGTCCGCGCAGCGAGCTGGGGA  
AAG

The following amino acid sequence <SEQ ID NO. 211> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 83:

FPSSRCADSPRSLAPRRNACPRKGGGREREGEESRSGEGGRRARWSAEKAEKRDEGERAEGKDRRERG  
REFLGPFPFTRSVWQVPRRPRTGLAKPHRLLPGLPDQGHAEVGCPEATPGQAEKEGTRDFHASGNITVG  
WATSAAIRESPLPQAWPLPRSII

The following DNA sequence Seq-2542 <SEQ ID NO. 84> was identified in *H. sapiens*:

AAATACAGGGATACATAAAGGAACCTCAATCCCTGAGGCACACATTGTCTAGTAACATATTAGCAATGGGAG  
ACAGGGTGTATAGAAACAAAGGGCTGGAAGCATTTATTTTCTGATGTCCCTGGGTATGATTTACTGACT  
GGTTTTGCCCTGAGCAAGTACTAAGTACAAAGATTTTGTGCAATACATGGAAAAATTCAGCAATTGTGT  
TATGATTGTTGCTATTTACTTTATTGTTATTGCTTCATATGAAGTAGCCTGTGAATAGATCTAAAAATTTT  
ATAGCATTTGATGGTGAAGTTGGATTTTCTGTCTGTCAATTTTACTTGAATAATCTGCTTCATTACATTC  
AGGGTAAAATACATAGCTGAAAAATAAACCGACGAAGAGAATAAGGGTAATATGCACAGTCTTAAAGCTCT  
GTCAACTCTCAACCCCTAAAGTAACTGTTGGTGCTAGCCAGGATTTCTTCAAAAACCAAAAGCACTGCTT  
ATGTTCAAAACACTTGACATCTTCGGAACCTCGCATATAAGGTACACCACATGCAAGAGTCACTTTTACACA  
TAAAGTTTATAATAATGATTTGGTTTCATATTTGGTTACAGTGACAGATACTCTTTTTTCATAAACCTGTG  
GGAAGACCAAAATCCATCTCCGTAGTTTGCAGTGCCTCTACTGCTGACTTTCTCCATAAATATTTTAACT  
GTGCACGTTTCT

The following amino acid sequence <SEQ ID NO. 212> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 84:

KYRDTRNLNPGTHCQHISNGRQGVIEKWKALFFCPWVFTDWFCEQVLSTKIFVAIHGKIQQLCYDCCY  
LLYCYCFISSLIDLKILHLMVKLDLFLFCQFYLNLLHYIQGKIHSKINRRREGYAQSSSVKLSTPKVTVGA  
SQDFFKNQKHLCSKHLTSSELAYKVHMQESLLHKFIIMIWFIFGYSDRYSFFINPVGRPKSISVVLQC  
LYCLSPIFLCTF

The following DNA sequence Seq-2543 <SEQ ID NO. 85> was identified in *H. sapiens*:

GGAGATTAGCAGCAATTAAGAGAAGAAATCCCATTCATATGAGTGATAAAGCAATTAAGTAGAATAACTT  
AGAAAAGGTTCTTGGAGAGTCACAGGACAAAATAGCATAGGTACGGTTTCTCTTAATTGAGCTGTTATAAT  
TTACAAAGCAGTAGAAAACAAATACATGAAAAAGTATGTGTAACCTCAATAGAGTTTTATTTTGAATGCA  
GAAATCTTCAATGAAATGAATATGCCTCACCATTCTAGCTTTATTCTTATCCCAAAATATCAACCACAG  
ATGCATAGGCTCCAGGGAATCTTTTGCCTGACTAGAAAACCTTATTTAAGAAACAGTACCTCTAAACACA  
TATCCTTGGGCGATTAGTCTCCTGTGAAACAACTGTTATTTCTACACATCTATTTAGAATAAACTTGGATG  
ATTGACTTTTGGAAATGTTCTCATTTTTTAGAATAATAGAGATGTAGGAAAAAGTGAAATGCTCTGTCTGTA  
TCTATTTAAGTCTCGACAGCATTAAAGAAATTTATTTCTTCTCTGCAATCACTCAAATCTGAGCACAAAA  
CTGAAATAGCATCGTAAACTGACAAAGCTCAAGGTTAA

The following amino acid sequence <SEQ ID NO. 213> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 85:

YPALSVYDAISVLCSDLSDCRKRINFFNAVETLNRYRQSIFTFYSYISIIILKMRTFQKSIIQVYSKMCRRNS  
CFTGDSPKDMCLEVLVSIRFSSQAKDSLEPMHLWLI FWDKNKARNGEAYSISLKISAFKIKTLLKLHILFS  
CICFYCFVNYNSSIKRNRTYAILSCDSPRTFSKLFYLIALLSLIMGISSLNCCS

The following DNA sequence Seq-2544 <SEQ ID NO. 86> was identified in

*H. sapiens*:

TTAAAGGACAGGAAAAAGAAATGCCATGTGAACACTAATCAATATAAAGCTGGAATAATTTTGCTAAAGCG  
GACAAAACACTTCAAGGCAAGGAAGTATTACCCATTCTGTGTCAACCTCATTTTTATATCATTATTTCATC  
TCTCATATGTGTCTATCTGGTATCCCCAGCCATAATCTGGTAACCTATCTCATCACACGCCTTTCTACCCA  
GTGTTTTGCCACAGGAAATGCTCAGTATATGCCAGTAGTCTGGGTGTCTCTGCAGATAAGTTGTGTATT  
ATCAAAATGCCTGACTTTATTCTCTGTTCAAAGCTTCTCTGTATCATGTGGGTATGATTTTGAAAAGTGT  
AATGTTAAATGTTTAAACATATTCCTCAGACCCACTGCTGAGGAATGTCCTGCGGAGGACAGTCTAGA

The following amino acid sequence <SEQ ID NO. 214> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 86:

RTGKRNAMTLINIKLEFCSGQNTSRQGSITHSVSTSFIFISLMCLSGIPSHNLVITYLITRLSTQCFAR  
RKCSVYASSPGCLCRVYYYQNALYSLFKASLYHVGMLKTVNVKCLTYSSDPLLRNVLRRTV

The following DNA sequence Seq-2545 <SEQ ID NO. 87> was identified in *H. sapiens*:

TTCATAATTGTGGTAAGGACCTCTAGTCACAGGGACCTGGTTAATATCAGTATGCCTCATGTTATTTGGGA  
ATGATGTATTTCAAAAAGTTTATTGTGTAAATAATAGAAAATTGGCTATTTATACCTAATATACTTAATTT  
TTAATTGTTTATTGGTTCTTTTAAATAAAATGTATTATATACTTTCTTTGAACCTTGTTAGACCTAAAATAG  
TTGAACCTTTTTTTGTTTTTGTCTTTTGTATGACCCAGGGTCATAATTATAACATTAATTTCTATATTGTAT  
CATAATAAAAATATACAGAATTATTGCTGCATAACCATATAACCTCCAGTTCTGCAGTTTTGTGTTATCT  
CTCCTTTACTGCTGTTATGCCCTTGTCTGCTTTTATAGCTTTCTCAGACCTCCTAATTTTCTCTTCCAG  
TATGCCTATACTTTGGGAGATCAGTCATCAATTTGTTGTGCTTAAAATAAGAACAACTAGGGTTTGAGTAA  
GGACCTAGCAGCCTCTTCTGTGAGTAAAGTGTGGGTACTTTAGTGTATGGACTTCAACATGTATTCTGACA  
GCTCCTAAACTCCTTCTGTTTAGGTCTCACTGGGCTGTGTAGCTACTTGATGTCACCAGATAACTAATCTC  
CTGATAAGTGAAGTGAAGTGGGTTGGAGTTTGCCTATGTCGACTCCCTGTTCACTGATGCCC

The following amino acid sequence <SEQ ID NO. 215> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 87:

HNCGKDLSQLPGYQYASCYLGM MYFKFV I IENWLFIPN ILN FLFIGSFNKMY ILSLNLVRPKIVEPFF  
VFAFDDPGSLTLISILYHNKNIQNYCCITIPSSSAVLCYLSFTAVMPLSAFYSLRPPNFPPLPVCLYLGDO  
SSNLLCLKEQLGFEGPSSSLFCESVGTLVYGLQHVFPQLLNSFCLGLTGLCSYLMSPDNLPDKSVTGLEFCLC  
RLPVHC

The following DNA sequence Seq-2546 <SEQ ID NO. 88> was identified in *H. sapiens*:

CAACTGATTATACCCAGGAGGAAAGCGGACAGATGGATTGACATGAATAACGTCATTAGCCTCTTTGCCT  
CTGAGAAATTAGAAACAGGGGAGAAAATGCAATAAAGTGTTTACCCATAGACTCCACAACGTTAGGGTCGG  
GTAATATTTTGGTTGCTAAATATTGCCAAAAGATGATTTACTCTTTATTACATATTCTTCCATTTCTTT  
TGTGAACCTGGCTATGAATTCCAAAGTGAATCTATTAGAATTCAATGGATCATCTTGTGACCACACTCAGG  
GAATCACAAATTATACACATTTATAGGGTACTGCTCTGCAACATAAACAACATTGTGACAAGGGACCTG  
CAACAAGAAAAGGAAGAGATTCTTTAAATGTTCAAAAGGATAAAAAATAGAAAAGAGAAAAAATTTTAAT  
GACAAAAGTATACATCCAAGAGAGAAAACAAATGATAAAACAGAATGAAGAGGGAGGGAAGGGGCAACGT  
TAAGAGAGGGTCTGATGGGAGATGAGCGATATTTATGGGGCTAATCCTCCCTCTTTGGGCTCATTATTGC  
CTTTCCCTGTGCTCCCCAAAGGCTCCCGCTGGCTTGTGTTTACAGATGCATGTTTATTCTCCCTGCAC  
TCAGCTGTCAGAACTTCATCTGTT

The following amino acid sequence <SEQ ID NO. 216> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 88:

NLYPRRKADRWIDMNNVISLFASEKLETGEKMQSVYPTPQRGRVIFWLLKYCQKMYLLFITYSSISFVNWL  
IPKNLLEFNGSSCDHTQGITIITYTFIGYCSANINNIVTRDLQOEKRRFFKCSKGGKREKILMTKSIHPRE  
KTNDKTERGREGATLREGLMGDERYLWGSSLFWAHYCLSPVAPQRLPGLCSQMHVYSPCTQLSETSSV

The following DNA sequence Seq-2547 <SEQ ID NO. 89> was identified in *H. sapiens*:

ACTCTTCCTTTGTCTCTTTTCAGCTTCTGGTGGCTACTGGCAATTCTTGGTGTCTTGGCTTGTGGACACA  
TCACCCCAATCTCTGCTTCTGTCTTCCCATGGCCATCTTCCCTATGTCTCTGTCTTCTTCTCTCTCTTA  
TAAGACATCTGTCAATTAGATTTAAGGCCCATCCAATCCATGATGATCTCATCTCAAGATCCTTATCTTAAT  
TATGTCTACAAAGCAGCTTTTCCAATAAGGTCACAATCTGAAGTCTAGGTGAACGTATCTTTGGGGGCA

AGGAGAATGCTATTCAACTTGCTGAAAACAACCTTACCTTGTTTTTTCAGAATACTAAAACATGCTTCAGTATG  
CATGTATATAGTTAGGTGGATTATAGATCATATTATTTAGTTTTTAACCAAATTAATCTTCACAAAATACA  
CAAGTGGATCAAAAAATTTTAGGCAAAAACACCCACATATTGAACACAGCAATCGCACAGCCCAAGAGA  
ATAGGGAAATTGAAAGGCTGACTTTTATCCCATCCTCTGTATAAGCTCTTGTGAGCCATTGAAAACGTC  
ATAATAACATAATCATACCTAAT

The following amino acid sequence <SEQ ID NO. 217> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 89:

SSFVSFSFWLLAILGVPWLVDTSPOSLLLSSHGHLPYVSVFFPVSYKTSVIRFKAHPIHDDLISRSLSLC  
LQSSFSKGNHLKFVNVSLGARMLFNLLKTTYLVFRILKHASVCMYIVRWIYRSYYLVLTCLIFTKYTSGS  
KNFRQKHPTYTQQSHKPKRIGKLGKLLSHPLYKLFVSHKLPNHT

The following DNA sequence Seq-2548 <SEQ ID NO. 90> was identified in *H. sapiens*:

AGTTGTGTTTGGTTGGTATTTTGGAAAAGATCTGATAGAATTCCTTGATGGACTCATACTTGGGTAATCAT  
TGAAGAGCAAGTCACTGTGTAGGGGCTGGGTGAGATGAGTATACAAAAGTAAAGAGAACCTGACCCCTCTG  
GCCAAGACCTTCAGAAGCTCAGAGTTCACGTAATTTTCATAAAATCAAGTGAGTAAGGGTTACAGCAGCA  
ATGAGATGTTCTTTTGCTTTCACACAGATGAGGCCTCCATGAATGGGGAGTAAGAAGAAAAGGTTTCACA  
AAGGAGTAGGCCTGTGAGCTGGGCCATGAAGGGTGGGCTCTGATCTATCAAGCAGAGCAGGGGGAAAGCCC  
TCAAAGCAGAAAGAGCAAAGCTGCATGGTGTGAAGACTGCATGTGATTCAGGAACCGTGAGCAATGGTAGA  
CTCGTGCCAAAGCACAGTGTGTAAGGAAGACAAGGCTGGAAACGTATGCTGAGGTCTGACTGTGAGAGTTT  
GAAGCCCCACTGAGAGGTCTGCACGAATTAAGAATTTACAGAGAAACATGATTAGTTCTACAATTGGAAAAA  
TAATTCTGGTGCTAAGAACTAGTAAGGTATAAGATAAGCCTAATCACGGAGTGATTTGAAGT

The following amino acid sequence <SEQ ID NO. 218> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 90:

TSNHSVIRLILYLTSSHQNYFSNCRNHNHSLKFLIRADLSVGLQTLTVRPQHTFPALSSLHTVLWHESTIA  
HGSITCSLHTMQLCSFCFEGFPALLDRSEPTLHGPAHRPTPLNLFLLPIHGGLICCESKRTSHCCNPY  
SLEFYENYVNSELLKVLARGSGSLYFCILISPSPHSDDLFDYPSMSPSRNSIRSFPKYQPNNT

The following DNA sequence Seq-2550 <SEQ ID NO. 91> was identified in *H. sapiens*:

GTGGCTGTGCGTCTCTGTGCAGAAGAGGCTGCGCGGTGCGCATGGGGCGACTGTCCAGGAATCCCTGGGGC  
TCCTGACCGCCACCTCCCAACCCCTGCCAGGCCGGACACCTCGGTCTGGCTGCCAGGGCAGGGGCGGGCCC  
TGGCCTGGCTCGCTGGGGCCTGGGGAGCTGCCCCGTGCTTCCAGCCAGTCTCCCCCTGGCTGTGCCGGCT  
GCTGGCCACTCCACCTCCAGGCTGGCGTGAGGCCCACAGCTGCTGTTGCACAACCTGGTTAATGTGT  
GATGGGGGAGGCTGGGCTGGCCGCCCTCTGCCAGGGCTTACAGCCCTGCCAGCCCAAGTATCTG  
AAGGAACACAGTGGAGCCAAGCCCGCATGTGGAGAACTCAGGCTTTCAGGAGACCCTGGCCCTGCTCCT  
GGCGGCTCCGGGTGGCTTTCAGTCTC

The following amino acid sequence <SEQ ID NO. 219> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 91:

WLCVSVQKRLRGRHGATVQESLGLLTATSQPLPGRTPRSGCQGRGGPWPGLPGELPVLPAQSPPGCCRL  
LATPTSQAWREAHSCCCTTLNVNWGEAWAPAPLPGLQTPAQPYLKEPQWSQARDVENSQFQETLALLLA  
APGGFQL

The following DNA sequence Seq-2551 SEQ ID NO. 92> was identified in *H. sapiens*:

CTTGCTGGCTTTCTTCTCCTGGGGGCTGCAGTGCTGATTCCCTCTCTGGTTGGCTTAGGCTCCAACCAGC  
TGCAATTGTCTGTCTTCCAGAGAAGAGTATAGCTGATGAGCCTGGAGCTCTGGGAGAAAGAGAGCACACAG  
AATCTTTCTTGACCATCAGTCCAGCAGAACTACATTTGGAGCGGCCACACCTATTGGTCTTAAGCCAC  
TGCTCTCTTAAGAAGGTTGAGTGTGGGCTGCCCCAGGCACATAGTAAGATGTCACCAGTAGCTAAGGC  
CCTAGGGCCTGACAGCAGACCTTC

The following amino acid sequence <SEQ ID NO. 220> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 92:

LAGFPSPGGCSADSLSGWLRQLPAAIVCLPEKSIADPEPALGEREHTEFLTISPAESYIGAATPYLVLSH

CLSEGVLGLPQAHKMSPPVAKALGPDSRPF

The following DNA sequence Seq-2552 <SEQ ID NO. 93> was identified in *H. sapiens*:

AATGTTTATATTATAAAGTGGAGTAGAAAAATAAACATTAAATACTAGAAAATGAAAGTCAATAATGCT  
GAGTGTCTTTTTTAATAGCACCAGGTACTGTTTTAAGCACTTTATAAAAAAGATACTATAAAATATATAAG  
CCACTGAGGTAAGTAGTTGTAGAGCTGGGAGGAGCTGGGATTTGAACTCAAGTACTCTGATTTTCAGAGAAC  
CTGCTTTTAATTTTTATGCGATACTACCTCTTCAGTAAGATAGCAACTATTTAAAAACAATACGAAAGCAC  
ACCCACATGCACAGCAGTGAAAAAAACCCATCATGCAGTGTTCATCAAGAGCTGCAGTCTATTTCCCC  
ACCCCAAATCCAAGGTGGCCTTGTGACTTGCTTTGAAAATGAAATGCAGTGGGAAGGAATTTTGTGTGACT  
TTCCAGACTAGGCTGCAAGAGACTTTGCAGATTCCTCCATTCTTGGAAATGCTGCCCTGAGATAGCC  
ATGCAAGGAAGATGGTCTACTCTACCAGGGGATGAGAGACCTGTGGAGGAGAATTAAGGTACCCTTACCC  
CAGCCAGAAGCAACAGCCAGACATGTGAGTGGGGCTATCCTGGGCCTTCTCCATTTCACCAACCCAGCGG  
CTGAATGTAGTCACATGAGTGAGTCCAGGTG

The following amino acid sequence <SEQ ID NO. 221> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 93:

TWTHSCDYIQPLGWLKWRPRRIAPLTCLAVASGWGKGLILLHRVSHPLVETIFLAWLSQGSIPRMWKGNL  
QSLQPSLESHTKFLPLHFIFKASHKATLDFGVGKTAALDENTAWVFFHCCACGCAFLVFLNSCYLTEEVS  
SHKNKQVLNQSTVQIPAPPSSTTTYLSGLYILYLFYKVLKTVPGAIAKKDTQHYLSFSSILMFYFSTPLYNI  
NI

The following DNA sequence Seq-2553 <SEQ ID NO. 94> was identified in *H. sapiens*:

ATTTTAGTGACATCCAATTCATCAATTTTCCCTTGTGGATTATGTGTGTGTCATATACCTGTTTATGCATT  
CATGTTCTAGTCTTTCCCCACGGAAAAAGCTACATTCATTATGGTAGCACACTTGTCTATCTAATCTATT  
TGTAATCACAAGCAGTCTAGAAATTGTGCCTGGCACACACTAATGATCAACAAATTTATGCTGAATGGAA  
TAAATAAATGAATAAACTAATTTATTAGGTAAACATTTTAAGTAAGTCTTTTTCTAACACTGGGGA  
ATGATAACAGTAGTAAAGTGGCATATTAACATTCTGCAAAATGATTTTAAATCCATTATTCTCTTGGGT  
TTCATACATCCCCTGTGGGGAGGACAGTTCAGGTATGATTCTCTTACT

The following amino acid sequence <SEQ ID NO. 222> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 94:

SKRIIPELSSPQGMYPREWINHFAECYATFTTVIIPQCKDKLLKMFNKLVIHLFIPFSINLLIISV  
CQAQFLDCLFTNKLDSKVCYHNGMLFPWGKTRTMHKQVYDTHIHKGLMNWMSLK

The following DNA sequence Seq-2554 <SEQ ID NO. 95> was identified in *H. sapiens*:

GCATGTATCCTCATCCTTGGAAAAATAAACTTTCTGAATTAAGTGGAGACCTGTCTCAGATTTTGGAGTT  
CACAAGTGTCTTTCAGCTCCTTATTCATTTCTTCAAAAGAGATGCAATATTATCTTAAAAATCCTCAAAT  
AGTTTACCATTCTCAAATACCAACATGAAATTTCACTTTACTACAAAGCCCTCCAATCGCCAGCAGCTCTC  
CATCATGCTTAAGTTCACTTCTTTCTATACAACCTTTGCCCTATTTCTTCTCTCTCAATAGAAAGCAAGTC  
CTCATTTATCTAATCTGGGCAATTGCTCCATTGGTCTCCCTTCATATTTCTCATATCTTAACAGCCTTTAT  
TGACTATTTTTCTTTTGGAGTTTACTAAAAATGGTTCATATTCTGTACCCCATGCAAAAATCTCCCTTTC  
TAGCACAAACACACTAAAATACTTCTTTGCTCTGGGTTTCATTTTTAGAAAGACTTTTATACTTCACA  
TGTCTCCATTTTCTTATCTGC

The following amino acid sequence <SEQ ID NO. 223> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 95:

HVSSSLEKTFINGPVSDFWSSQVFSAPYSISFKRDAILSKSSNSLPFSNTNMKFHFTTKPSNRQQLSIMLK  
FTSFYTTLPYFFFSQKASPHLSNLGNCISIGLPSYFSYLSLYCTIFLLSLLKMHVILYPMQKFSLSSTHT  
KILLCPWVFIFRRLFILHMSPFYSYL

The following DNA sequence Seq-2555 <SEQ ID NO. 96> was identified in *H. sapiens*:

AGGCCTGGAGCCTGGCTGGCCGGGCCATGCTGCTGGAGGTGCAGGGCACACCCGTTCTGGTGTAGGGCT  
GGCATGCCAAGTGCAGTGCAGGTGTCCACCAACTCCTTCTGTTTCCCTGATGTGGCCGTGGGGCTGTTT

GCCTTCCCCTTTGCCATCATCATCAGCCTGGGTTCTGCACTGACTTCCACAGCCACCTCTTTCTTGCCTGC  
 TTCATGCTTGTGCTCACACAGAGCTCCATCTTCAGCCTCCTGTCCATGGCCATCAACAGGTACCTGGCCAG  
 CCACAGTCGGCTCAGGCATAAAAGTTTGTACTGCTGGGACCCAAACAAGAGGGGTTACTGCTGCTCTGCTGGG  
 TCCTTGCCTTTGGCACTGGACTGACCCCATTCCTGGAGTGGAAACAGTAAAGACAGTACCTCTAATAACTGC  
 ATGGAGCCCTGGGATGGAACCATGAATGAAAGCTGCTGCCTTGTGAAGTGTCTCTTTTCTGAGTATGCGGTACC  
 CATGAGTTACATGGTATATTTTCACTTTTGGGGGGTAAGTCTGCCCCCACTGCTCGTAATGTGGCTGATCT  
 CCATCAAGTTCTTACAGTACTGCAGGCAGCTTTAGTACACGGAGCTGATGGACCACTCAAGGACCACCC  
 TCCAGTGGGAGATATACACAGCCAAGTCGCTGGCTGTGATGGTGGGGGATGTTTGCTCTGTGCTCGCTACC  
 AGTGCGC

The following amino acid sequence <SEQ ID NO. 224> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 96:

RPGAWLAPCCWRCRAHPFVVLGLACQVHCGCPPTPSWFCGRGAVRLPLCHHHQPGFCTDFHSHLFLACE  
 MLVLTQSSIFSLLSMAINRYLASHSLRHKSLVTGTQTRGVTAFLVWLAFGTGLTPFLEWNSKDSNNCM  
 EPWDGTMNESCLLVKCLFQNAVPMVMVYFSFGGVLPPLLVMWLISIKFFTVTAGSFSTRSWTTQGPSSG  
 RYTQPSRWLWWGMFALCSLPVR

The following DNA sequence Seq-2556 SEQ ID NO. 97> was identified in *H. sapiens*:

TATTCAAGAACTAGGGTTCATGACGGTGCTTCTGTTGTTACCTAGTAGAAGTAGCTTTGTAAGCACAAAGA  
 TTGTAGTTTTGTGAAGCTATCTAGTACAGAGTCACTCTGGAAGTTTAGCATTATAGAGTTTTTTCATAGAA  
 AGGATGGATAGATACAAGTTTTTCCTAACAAGCACAAGTGGCAGTCTTTGAAAATAATTTTTTATGTGTA  
 CATTGTAGCATTGGAAGATAACTGTGGTTGAGTGTGATAAACTGAACTTTTTAAAAATCTATTATTTTT  
 TTTACAAGTTAAGTTAGAGCCAGATATGCTGATTCTCTACCATTTTCAAAGAGGAATTGGAAGGGGAGA  
 GCTTGTATTATGTGGTATTACAAATAGTGTCTGCTCCTGAAGAAAATTTTGGAAAATCTCATGAGTGTCC  
 TCAGACTGAAAACAGGGATCCAGTCTGTTTTCATGCAGGACTCAGGAGGCGAGCGAGCATGTGATACCAG  
 GAAGGGTCCCATCCCTGCCCTGCTGGGGAGCCCTCAGTGGCGAGGTGGCGAGTTTCAAGCTTCACTTCAGAG  
 CATGGATACTGCTGCATAGGTGCTGGAAGGGTGTGTCATGGGTGCTGGAAGCTGCTTGGCATAGTGCATGT  
 CCTGTTTCTCTG

The following amino acid sequence <SEQ ID NO.225> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 97:

QETGHALCQAASSTHAAPFQHLCSIIHALKSLNSPPRHGLPSRAGMGPFLVSHARSPPESCMNNRLDPCFQ  
 SEDTHEIFPKIFFRSRHYCEYHINKLSLFQFLFKWRISISGNSLTCKKNRFFKKFQFITLNHSLPLMLQC  
 THKKLVFKDCHLLGKTCIYPSFLKNSIMLNFSQSDSVLDSFTKLQSLCLQSYFYVTTEAPSTLVSE

The following DNA sequence Seq-2557 <SEQ ID NO. 98> was identified in *H. sapiens*:

CTGTAATAGTTAGCCTGATAAGCGGAAAAGGGAAATGTAAGACTCAAATTATTGGTTCATAAAATAAAGCT  
 CCAGACAATTCTGTTTTATTATACAGAATGGATTGGTTGTGGTCTGTTAGCAGGCAGAGACACTATGCATA  
 CAGATACCATAATAATAGTAAAGAATGGTTGAGTGGAGAACCAGTGCCTCTGTTCCAATTATTTTTATAAT  
 TGCTCTCTATCTACTATCTCTACAGATATTCATAAACAGTGTGCAACACTAACTCCATCCTTTCTGTTGCA  
 TTTGTTATTATTTTTGCTATAGACAAAATTTCAACCATGCAGAAAACAAAAGTTTAAACCGTTACATTGT  
 TCTCTGCATTTACAGGTTTGCAGTAATGTAGGGTAATTAGACATGCTGTTAAATGACCAAATTAACACAT  
 CATGTTTTGGTAAAGAAACGAACCAAGAAGTAGTAAAGATGGTGGGGAATTCCTGAATCCCAAAGCCTT  
 CTTAATTTTGACCATTTGGACATTCATATATGTGTGTGTGTGTAGTAATCAAATCAGAAAACAACCAAAA  
 GGGGCCAGCTCTCAAATCCAGGCACCTTAGTGAGACAAAGGC

The following amino acid sequence <SEQ ID NO. 226> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 98:

LCLTKVPGFELAPFGCFSDLNYYTHTHIMSNQNEGFWDSGIPHHLYYFLGSFLYQNMCLIWFSNMSNY  
 TLLQTCCKREQCNGFKLLFLHGKFLQKQMRKDGVSVAHCLWNICRDSRRRAIKIIGTEALVLHSTILY  
 YYGICMHSVSACQTTTNPFCIIKQNCLELYFMNQFESYISLFRSLGLLQ

The following DNA sequence Seq-2558 <SEQ ID NO. 99> was identified in *H. sapiens*:

TTTTCTGCAAAAGACCCCTTTATAAATAAGTAAACAGCTACTGGCTCAAATTTCAATTGTATTCTTCTGG  
 ATTGTGTTTTTTTAAATTATTTTTTTCGCTGTTGTCACTGAGCCCTTCCATGTCTCCGAAATTCACACCTTCC



ATGCTTTTACAATAAGAGTCTGGCCAGTCATGGCCCCACAAATCTATACACCATACCCCTGTTGGTTCAT  
 TTTATCAACTTATTGGTCTATTTCAAGTCTGTCTTTTACTTGAGAAAGAAGAGAACTTCTCTGTTTACAA  
 GGATCATATAGTTTTACCTTATACAAGTACGTAATTTGTCTATATTGTCTATTGTTAATGTATTTCATACCA  
 TTGTACCAAGTAGCCAAGACTGGAAGCAGTCCCCATAGGCCACCCCCACAGTTTGGGAGGGTTGTGAGACA  
 AAGTTATGGGATACTTAGTCAACCACAAACTCTGGCTTGAAACTTGTCTCCTTCTCCCCCAAGTTCCTCA  
 GGAATGTATAGTCACTGTCACTGCTGGGTTTACTTCTGTTATTTTAAAGTGTGTGATGTGAGTTTCCTT  
 AGAAAAGCACCTGACAGTAATCTAGTTCAT

The following amino acid sequence <SEQ ID NO. 227> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO.99:

FSAKDPFINKTATGSNFCILPGLCFFNYFFAVVTEPFHVSEIHTFHAFTIRVWPVMAPQILYTIPLLVHF  
INLLVYFKSVFYLRKKRNFVYKDHIVLPYTSTFVYIVYCCIHTIVPSSQDWKQSPATPTVWEGCQTKLWD  
TSPQNSGLKLVSFLPQVPQECIVTVTAGFTSVIFKCLCEFPKSTQSSS

The following DNA sequence Seq-2559 <SEQ ID NO. 100> was identified in *H. sapiens*:

TTTTATCACCCACAAAACCTTTATAATCTGTCACTTGACTCATTGGTTGCCTATTAGCCCATTCCCAAGACA  
 TACTCCTGAGAGCAGGCCACTGTAAGGTCATACAACCTAAAACAAAGCCACAAAGAGCCAGAACCTTTTATA  
 TTTAGAAAAAAAATGTGCCAGGATGTATAATTCACATTAATGCCATTGTTGAAAGCCAAATAAATACA  
 TATATATGTCTAGTGCACAACCTACAGAAGATATCCTTAATCTACTTATACTGGAAACATACTTACAACAA  
 AGGATTTTGTATGGACATAGCGTGAGTTGTATTTTCAGCTTTAATGAAAGATCTCATGCCAATGACAAAAAG  
 ATTTCCAAAGCAGGTAATGAAAGCTATAACCCAGACAAATATTCTGAGGATATTGTTAGCCAAGAGGTCCT  
 CAAATGAAGAAATGCCGTCCGTCAAGGGCATAATATTCGGACATGGGGAGCATAGGAGCAGTATCGAAAG  
 TTTTGAATAACTAAAGTCAAAGGGAAAAAAGTGTCACCTTGCAGCAATGATACAGAACCTACAGTTGC  
 AGTCCTAT

The following amino acid sequence <SEQ ID NO. 228> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 100:

RTATVGSVSLQLQSDTFFPFDFSYFKNFRYCSYAPHVRICMPLTDGISSFEDLLANNILRIEIVWVIAFITCF  
GNLFVIGMRSFIKAENTTHAMSIKILCCKYVSSISRLRISSVSCALDIYMYLLAFNKWHLMIHHPGHIFFS  
KYKSSGSLWLFCRLYDLTVACSQEYVLGMGATNESSDRLSFVGDK

The following DNA sequence Seq-2560 <SEQ ID NO. 101> was identified in *H. sapiens*:

CAGCACTTATTCCTCGCTGCATGCTGGTGTCTCTCAGGACAGGGGAAGTCTGCTTAGAACTGGCCGGTGCC  
 AACCTGCACTGGCACTGCTTAGTAGGCCAGTGCCAACTGGGATTCTCATGGCTGTGTGCTCTGTGCTCAC  
 CCACCTGTGAATCACCGGGTGGTACAGAGTGACAATCCATCAGCTGTTAAGATAAGATGAATGCAAAAAGG  
 ATGACATTGCCAAACAGACTGTTGGGTTATTTGGAGGTATCTGTATGACAACTCTAACCCGAAATTTTATA  
 TTTGGCACAGCCATGGCCTGTGGGATGGCTGGCATTCTGGATATGTTGGAAACAGCAGCTGGTAGCATG  
 GAGCAATGTCCAAGTGCCAGCCCCACTCATCTGCTACACGTGCTGTGCTATTCTGCTTCACTCGCACAAAA  
 CTAGACTGCAGCGCAATATACCGGCTCATCCTTGTGTGGTTCTCCAGCACTCACGGGCAATTATTTCTCCA  
 TTTCTATGTGTTTTAAACCTGTTTTCTCTCCGACCTGTCAATGAGAGCATGAACCTTTATGAACCCACCT  
 CCCTGGACCCTCTTGATAGGTTTCGTGGAAGTGGAATCATTCTAAGAAGCAGTGAAGGCAGGGTGCTGTTT  
 TCTGCTTTCACAGCTCTG

The following amino acid sequence <SEQ ID NO. 229> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 101:

ELKQKTAPCLHCFLEFHFHETYQEGPGRWGSFMLSITGRRENRFKTHRNGEIIARECWRTTQAGILRCS  
LVLCESTRIAQHVQMSGAGTWLLHVPVLFPTYPECQPSQAMAVPNMKFRVRVVIQIPNNPTVCLAMSSF  
LHSSYLNSWIVTLYHPVIHRWVSTEHTAMRIPGWHWPTKQCQCRLAPASSKQTSPLVLRDTSMQRGISA

The following DNA sequence Seq-2561 <SEQ ID NO. 102> was identified in *H. sapiens*:

AGGTTCCACTCTGTTAGCTGAGTACACACATCACAACTTGTCTTCTCAGCAATCCTTCTGTCTCGTTTTTA  
 TGGGAAAGATTATACTTTTACCCTAGGCATCAAAGCGCTCCAAATGTCCACATCCAGTATACTACAGAA  
 AGAGTGTCTTCAAACCTGCTCTATGAAAGGGAATCTTCAACTCTATGAGTTGAATGCAGACATCAGAAAGAA  
 ATTTCTGAGAATGCTGCTGTCTACCTTTTATTTGAATTCCCGCTTCCAACGAAATCCTCCAAGCTATCCAA  
 ATATCCACTTGCAGATTCCACAAAAAGAGTGTTCAAAACCTGCTCTCTATCAATGGCAAAGTTCAACTCTG



KAFLLKILLAGTCYREDSIHKLTKYFPSYIFIFINSFLNDIYFWVFTHVLYMFLFSFTIEHTLYQPEASEHL  
MGAKNKKKTSFGIANTFHLCLIHIKFESWAYYFEHFH

The following DNA sequence Seq-2565 <SEQ ID NO. 106> was identified in  
*H. sapiens*:

GAATGATACAGCCACTTGGGGAAAAAAGGTCTAACAGTTTCTGATAAACTAAGTCAGTAATTCCACTC  
ATAGGTATTTCATCTCAGAGTAAGTAAAAGCGGTAGTCCATTAAGAACTTGGATAAGAAAGTTCACAGTAA  
GCTTTATTCAAAGACCCCCAAAACCTGATAACAACCCAAATGTTCCACCCAGAGAATGAATAACAAATC  
ATTCTGCATTCTTAAACAAAACAAAACAAAACAAACCCTCCATGGCAAACAAAAGGAGAAAATGCCTG  
ATACACACAACAGCATGGGTGAATATCAAGAACATTTGCTGAGTGAAGGTACAGTTATACAGTAGCGCATT  
CTGTATGGGTCCACATACAGAGTTCTAGAATATATAAAAAAACTATTCTAAAAAGGAAATAAAAA  
CAGTTGTATTGTTTGGGGAGGTGGGGA

The following amino acid sequence <SEQ ID NO. 234> is the predicted  
amino acid sequence derived from the DNA sequence of SEQ ID NO. 106:

PTSPNNTTVFISFFRIVFFLYILELCVCGPIQNALLYNCTFTQOMFLIFTHAVVCIRHFLLLFAMEWFECFV  
FVLFKNAEFVYSFSGWTFGLLSVLGSFESLLTFLSKFLNGLPLLLTLRIPMSGITDLVLSETVRPFFSPSG  
CII

The following DNA sequence Seq-2566 <SEQ ID NO. 107> was identified in  
*H. sapiens*:

AAAACATAAACTTTTGAACTCTTCTAAGAATGTCTAACACAAATTACCTGTATAGATATCATGGCACAG  
ACGATGCTGAGGCCGACTGACTGAAGAAGAACAGGCTGAAGATGCTGTACTCACACAGCAGCTGGCCCCC  
AGGTTACCCGCCCTTCATGTACATGGCGATGGTCACCTGGCTCACCAGCAAAGTGAACAACAGGTCCGTGG  
CAGCCAGCCGCATAACTGTGTAGAAGGTGGTCTCCTTCTGCTCCTTGCAGCGACTTGCACAGCACCACGATG  
GCCACCAGGTTGCCACCACCCCGAAAATGGACGGGTCCCAAGCTGTCCAG

The following amino acid sequence <SEQ ID NO. 235> is the predicted  
amino acid sequence derived from the DNA sequence of SEQ ID NO. 107:

WTAWDPSIFGVVGNLVAIVVLCKSRKEQKETTFYTVMRLAATDLLFTLLVSQVTIAMYMKGGPGGQLLCEY  
SIFSLFFFSQSGLSIVCAMISIQVICVRHSKSFKSFMF

The following DNA sequence Seq-2567 SEQ ID NO. 108> was identified in  
*H. sapiens*:

GCGTCTCTGCCCACCGCTCAAACTCTAATTCAGCTTCTTTATCTGCAAACAGGAAATGTAAACGTTTCT  
CGAGGAGTCATGAGTTCAAACAGGGTCACCGATAAGGGAGGGTTGGAACCTTTCAGAAGAAAATGCTAAAT  
ATGCCAAGGTGTCTATATTATTTTTTTCCAGCATATTAACTAGGGCTTAAGACCTGATAGCCCTGTGAGTA  
TGCGTCTGTCTCTTGTAGCAGCGCTGTTTCGCTTAACAGAGCCAAATTCAGCCCAGAGTGAGTCTTTGGTGT  
CCATCCCAGGCTCTGGCTACCATGTCACCCAGACGGCTGATTGAAGGCAGTTTCCTTCCAGGGACCAC  
GGCAGAGTGCCACAAGATTAGCAGAGAGTCTCGTCTCCAGCTTGTGACGTACGCTACAGGTCTTGGGATT  
TGCCAGCATCTTATAATTTGTACAATAAATGAAGCACCCATGCAGTGCACACACACAGTACACATGCTA  
TTAATCTATGAGTCTTGGGACTTGCCAGTCTCTTTTTTTTTTTTGAGACAGAGTCTCGCTCTGTACCCA  
GGCTG

The following amino acid sequence <SEQ ID NO. 236> is the predicted  
amino acid sequence derived from the DNA sequence of SEQ ID NO. 108:

SLGDRARLCLKKKKETGKSQDSNHVYVCVCTAWVLHLLYKIIRCWQIPRPVAYVNKLETRLNLANLVALCRG  
PWEGNCLQIRPSGHGSQSLGWTPKTHSGLNLALLSEQRCKYKQTHTHRAIRSALVNMLGKKYDTLAYLAIF  
FKFQPSLIGDPVTHDSSRRLHFLFADKEAELEFAVGRD

The following DNA sequence Seq-2568 <SEQ ID NO. 109> was identified in  
*H. sapiens*:

AGCACACGGACCACACCCCTAGAAAGAGAGTCAGCATTCACAGACATCAACCTGGCACCACAAAATCTT  
GGTCCTCAAAGAAAGATAAGATTGTATTTGGTAACTCTGATTCCTAAATAGGAAAAGGAGCCTGAGACAG  
ATTGATAAGATATTAAACAAGGCTGAAAATGAAAAAAAAAAAAAACTTCTGGTGGCCAGAGGGTTGA  
GTTGATCAAAGTTTGAACCTACACACTGTAAATCAAAGTTAATTACATTTTACTCCAGGTTGTATGTGGTG

GATTTTGTTCATCATTTTTACTTGTTCCTCGGTGTTCTCTTTCCCAGTGGAGCTCCTGGGGGAAAAGGGCC  
 AAGAGGTTCTAAGTTTCTCATATGGCCCCTAGCACCATCAACACAGGAGAGCACATCATAAATACCAT  
 TTGATGATTTTCTTCCCGCGCATTTCATAGCCCCAGACCCTGTGTAAAGGCTGCTGAGCAATATCATTAC  
 TGAAGTGCTACTCTCCCTGCAGGTTGGGTCCAGAAAATATGGTGCTCGGAAACACTGTAAAGCTGCCTC  
 TTTAATAAGGATCCTGGTGTCCCGTGATGGATGCTATAAACCTCAGACTGGCTGGTGTGCTCACAGCCAT  
 GTAGGACCATTAAACAGCGTCTGGT

The following amino acid sequence <SEQ ID NO. 237> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 109:

STRTPLERESAFTDINLAPQKFLVLKERDCIWTLIPKEKEPETDDIKQGKKKKKLLVAQKGVDSLNLYT  
 LIKVNYIFTPGCMWWILSSFLLVPRCSLSQWKLGEKGQEVLSFLIWPLAPHQHRRHHKHYHLMIFFPRIH  
 SPRPCVKACAIISFTEVLLSLQVGSRKYGARKTLKPLGSWCPVMDAIPQTGWCAHSHVGPLTASG

The following DNA sequence Seq-2569 <SEQ ID NO. 110> was identified in *H. sapiens*:

AAATAGTCCTTAGACTTGTAATACCTTGACTCGAAGGCAGATAAAGTGAACAGTATGAAAGCAAAAAGA  
 CTGGAATCAAAAGCGTTGCTTCTAAAAAAGGAGAGAAATATGTTCTTGAATCACATGAGGAGGAAGATA  
 ATGGGACAAACAACCTGGCTTCAGGATTTTTTTTTCTTTCTGAGATTCACACCAAATTTCTGCATGCTTGA  
 GATTTACTTTACCTAAAATTTTTAGGCCCAAATCAGTAGAACTCAATTGACTGTTTTGGGGGACCTTGT  
 CTGTCGACAGTGATTTGATTTAAATGGGACAATATGTGGAAGTCTGCCCTTTACTAGCTGTTCCAAA  
 TGTCAATTCATCTGAGCCTTCTTCTATAAGGGGACATTAATGTCTTTTCTGACATTTTCTCATGATT  
 GACATTTCCAGAAATTTCTCCCGAGCTATTAGCTTCAATACATTATTATGCAATTTGGTGGCATTCTTT  
 CCTCTACCTAATTCTGTAAGATCAGATAGTATTGTCTAGAGATAAACTTTTTCTTTTCTCATACAC  
 ACTCAGTACACAAGAAGCCAC

The following amino acid sequence <SEQ ID NO. 238> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 110:

WASCVLSVCMRKEKVYLNKYYLIFTELGRGKNANQMOC SLGRNFWECQSGKMSEKDINVPLKKAQMEITFG  
 TASKGQTFPQYCPPIIKYTVDRQGPQKQSIIEFLILGLKILGKVNKHAELWCESQKRKNPEASCLSHYLP  
 PHVITRTYFFSFRSNAFDSSLF AFILVHFICLRVKVFTSLRTI

The following DNA sequence Seq-2570 <SEQ ID NO. 111> was identified in *H. sapiens*:

AGGATTCACAATGACTGGGTAGTGCAGAGGGCGACAGGATGGCTACAAAGCAGTCATAGGCCATCATGGTC  
 AGGAGCATGTCTTCTATACATGCAAAAAGGACCAAGAAAGACATCTGTGTCAGGCAGCCCGCATGAGAGAT  
 GACTCTGCTATGCAACTGCATGTCCACAGTCATCTTGGGAACCGTGGCCGAGGTGAAACTGAGGTTAGCCC  
 AGCACAGGTTGGAGAGGAAGATACATGGGGGTGTGGAGGTGGGAGTCAGGTTGACAGCAGGATGATG  
 AGCAGGTTCCCTCAGCACCGTGACCAGATACATGGACAGGGACAGGGACAGCAAAGCAAGGACCGGCTGCAG  
 TTCTGGATCCCCTGAGAGTCCCAGGAGGAGGAATTCTCAGACACCTGTGAGACTCCGTGGCTCTGTGTGAC  
 TTGGACACCTTGAGAAGGAAGAAGATTGGAAAAATAAAAGACAAAAGCAGCCCTTCATGCTGAATGCAA  
 GCAATTCACAAGGGAACATTTTCACTTGCAGACCATACACCGCCAGCAATGTTTCTCAGTTGTGACAAA  
 TCCAAAATCTCAGAATTGTTACATGTTTTACTTTTTTGCTATTCAACTCTTCTGTACATACTACTTTAG  
 AGAAAATCCACT

The following amino acid sequence <SEQ ID NO. 239> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 111:

WIFSKVVCERVEQSKTCNNSEIFGFVTTEKHCWRCMVCKCENVPLIACIQHEGLLFVFFYSNLLSFSRC  
 PSHTEPSRLTGVEFLLGLSGDPELQPVALLSLSLSMYLVTVLRNLLIILAVNPD SHLHTPMYFFLSNLC  
 WANLSFTSATVPKMTVDMQLHSRVISHAGCLTQMSFLVLFACIEDMLLTMMAYDCFVAILSPSALPSHCES

The following DNA sequence Seq-2571 <SEQ ID NO. 112> was identified in *H. sapiens*:

ATTTCCCTGATGTTACAAATGAGCAATTGGATGACAGATGGTTAAATATTTTGATACTTGCAGCTAAAAAT  
 AAAATAAAATCCACCGGAAAAGGACCTTTGTATACATACCTACAATTATAGTGGTAGTGGTCTCCAT  
 GATTGTTTGTATGTAATAGATCAACAATGTTATCCAGGACCTGGGTTTCATGCTTTCTCGCCATTTTCGCTATC  
 TTTAGTTCTGGATTATCAAGATGGCTACAGCACTTTCAGCAATCATACCATGCTTGACACTAACTAGG  
 GAAGAATAGAGAATGTCTCTTTCTTTGAGTCTCTCTTACATCTTATTGGCCAGAAGTTGATTATCTGCCCA  
 TCTCTGAACCAATTATTGTGATGACAAATGAAGTATCCTTGGACAATGAAACACATTGCTGAAACTGGGT

AGAACTTCCCCCAAGGCACAAAGATAAAGAGGGGAAGGTGAGATAGCTAAACAAATCTGTTCTAGTATAA  
GTGGAAAAGGGGAGAATGGATACTTGGTAGACAAACCATAGTGTCCATTACTAAAAGATACTTGAGGGGACA  
ATGTACAGTGAATTAAAGTGATACAATTGCTAATGGGTTGAGTAATTACACATTT

The following amino acid sequence <SEQ ID NO. 240> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 112:

MCNYSTHQLYHFNSLYIVPQVSFSNGHYGLSTKYPFSPFPLILETDLFSYLTFFPSLSLCLGGSSNPVSMC  
FIVQGYFICHDDNNWFRDGGQIIKEFWPIRCKRDSKKETFSILPLVSSMVLKVLPSYESRRTKDSMARKHEPR  
SWITLLIYYIKQSWRPHYHYNCRVITKVLFGWILFYFLQVSKYLTICHPIAHLHQGN

The following DNA sequence Seq-2572 <SEQ ID NO. 113> was identified in *H. sapiens*:

GCTTCCAGGGATGCTGACAATGTTGTACTTCTCGACTTGAGTAGTGGTTACATGGGTGTTGCTTGTGAT  
AAATCATTGAGCTAAATGTGTTTATTTTCGTGTACTTTTCTGTATGCATGTTATATCTTACAATTAAGAAGT  
TTTAAAAAGAAGACTATTTACTGGCAAGGAAAGCATATTCCTGAAGTATTATGAAATGAAAAAGTTTACA  
AAACCATTTATATGGTGTGATCTCAATTTTACTCTATGAATGTACATATTTATACACATTTATATAAATTA  
AATGATCTGGAGTGATAAACATCCAGGTAAAATGGTAGTAATCCCTGGGTGCAAGCACAAAGTGTGTTTGT  
TGTTTGTGTTTTAGTGTCTATATATTTCTGATCTTTCTGTAATAAGCCTTTATTGCTTTTCTAATAAGAAA  
TAAAGTCATTTTGTAGTATCGACCCAGGAATAAGCCAAACAGATCGATAGAACAGAATAGAAAAGTGAAGAA  
GAGATTGATGATGTAAGAATTTGATGTGTGATAAAGGGGGGATTTGAATCAATGGAGAAAAGATGGG  
TAGTTCGATACATTTTGGTTAGTTCAATTGGCTAACC

The following amino acid sequence <SEQ ID NO. 241> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 113:

LANTNQVSNYPSFLHFKIPPFITHQILTSTESLSQFSILFYRSVGLFLGRYYKMTLFLIRKAIKAYYRKI  
RNITLKNKQTKTLVLAPRDYYHFTWMFITPDHLIYINVKYVHSSKIEITPYKWFCKLFSFHNTSGICFPC  
QIVFFLKLLNCKIHAYRKVHEINTFSSMIYHKANTHVTQTQVEKYNIVSIPGS

The following DNA sequence Seq-2573 <SEQ ID NO. 114> was identified in *H. sapiens*:

AATACCCCATACTATGGCACCTTGGCAGGCTGAATACTTTGGACTGAAGGAAATTGGAAAGGCCTCAGAAG  
CAAGCTCTTTCTGACCTTCTCCCATCCTCCTGTTCTCTGCTCCCTAAATCTAAGTGAGTCTTAAAAAC  
CAGAATTCCTCTTCCCAAGGTAGGTCATAAAAACTTGAACCCCTCTACCCCCAATCAAATCATAAAACCT  
ATAAATGTCACACTCTCCCTTCTCCCTTAAGACCCCTATTAGATGCAGGTCCCTCCCTATATCTGGGAAAA  
AGGCATCCTTACAGAGAAATCAAGAAGTATCTGAACAGAGAGGCCCTGCTGGTGTCCCCCTGCTGTGGTT  
TGGATATGGTTTGTGTTGGCCCCACTGAGTCTTATGTTGAAATTTGATTCCAATGTTGCAAGTGGGGTGTGG  
TAAGAGATGTTTGGGCCATGAGGGTGGATCCCTCATGAGTGAAGTGGTCCATTCTCACAGGAGTGAGTTC  
TCACTCTAGCTCCCAAAACAACCTGTTTGTGAAAAGAGCCTGATACCGCCTCCTCTCTCCCTCTTGCTTC  
CTGTCTGGTGTGTGACCTCTGTACACTTCGGGTTCCTTTGCCTTCTGCCGTGAGTAGAAGCAGCCTGAC  
GCTCTTGCCAGAGCAGATGCTAGTGCTATGCTTCTGGCATGGCCAGCAGAACTGTGAGCCACATTTTC

The following amino acid sequence <SEQ ID NO. 242> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 114:

YPILWHLGRLNLTDRKLERPQKQALSDLLPSSCSSLVSPKSKVLKTRIPLPQGRSKLEPLYPKSNHKTYKCH  
TLPSPLRLLDAGPPLYLGKRHPSQRNQEVSEQGLLVSPLLWFGYGLFGPTESYVEIFQCCKWGVVRDVW  
AMRVDPSVTWFHSHRSEFSLAPKTTVCKEPDTASSLPLASCPGVPLYTSGSLCLLPVEAARSQSRCCYA  
SGMASRTVSHIF

The following DNA sequence Seq-2574 <SEQ ID NO. 115> was identified in *H. sapiens*:

AATGTTAATAAAGAAGAACATATGGAGAAAACCTCTGTATTGCAAACATGAAGCCCATGTGCCTTCATCA  
TCCCCAGAACTCTGTCTGTTTCATGCTCCCTGGGATTCCGTTTCAGAAAACAAGTAAATGGTGCCTTCTGCAC  
ATTTATGTTAAACGGGAGAACCACAAAAGAGTGACTACCCCACTCCAGTGCTTGCTGGGGCTGGGAGAACAAA  
GAAGCTGCAAGTATGAGGTACTCAAAGACAGTGTACTAGGGTAATGATTTCCAGTATGGCCAAAAGACA  
TCTCTATGCAACCAAGCCTCACCTGGCCTTACAAAACAAGTGGTTGGCCAGAGCTTGAATAACAGCT  
GGGATGGATGGCCCAATGTAAAGGAGCAGGTGGCAGGCCAGTGGACCCCACTCTGGGGTGGCCCCATGGTG  
GACAGAGCCCTGCTCCCTAAAATGGCCAACACCTGTCCCAAGGAAGGCCACCTAGCCAGAAGTGCCCAACC  
ATCTGCTGTAATCAAATTTGCAATCACAGGTAACCTTTTCTCTCAAGGGTCCAGCTGGCAATATAAATAAA  
TGGAATGAATGGGGCTCCTCAGATGAGTACAGCATCTCCATGTATGGGAGCAGACATTACTGAGCTGCT

GCCATGTGGGAATCTCAGTCCAGTTGTGCCAGGTCTTCTGAG

The following amino acid sequence <SEQ ID NO. 243> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 115:

CRRTYGENSCIAKHEAHVPSSSPEVCLFMLPGIPFRKQVNGAFCTFMLNGEPKRVTTPLQCLLGLGEQRSC  
KYEVLKDSVTRVMIFQYQKTSMMQPSLTWPYKTKVWVPELEQLGWMAQCKGAGGRPVDPTLGWPHGGQSP  
CSLKWPTPVPRKATPEVPTICCNQICNHRFLSRVQLAIINGMNGAPQMSTASSMYGEQTLSCCHVGISV  
QLCQVF

The following DNA sequence Seq-2575 <SEQ ID NO. 116> was identified in *H. sapiens*:

TTATTTTTTATTTGATGATAGTTGAGAAATTTCTTCCAGCTTCACAACTTGTTATTGGAAATGTCAAGTGAA  
TTTCTGGACTGTTGTCTGAATTCGTTTGTAGGGCTCCCATACAAAATACCACAGACTGGGTGACTTATA  
CAACATGAATTTATTTTACAAATCTGGAGTCTGGATGTTTCATGATCAAGGTGTCGGCAGGTTTGGTTTC  
TTCTGAGGCCCTCTCCTTGGCTCACAGAAGGACGTCTTCTTGCTGTGTCTTCACATGGCTGTCCCTCTGT  
GTGTGTTTGTGTCCTAATCTCCTCTTCTTATAAGGACACCTGTTATGCTCCATCAGGCCCCATCTTAATGA  
CTCCATTTTAACTTAATTAGCTCTTTAAAGATATTTCTCCAAATACAGACACATTTTAAAGTACTGAGGA  
GGCGTTTTAACTTTATGAATTTTAGGGGGGACACAAATCAGCTTATAACATAACAATGTTATGTTTAAACAT  
AACAAGTTTAACAAACTTGCAAAAACATCTTTCAGATACTTTCATATTAAATTTTCTTGTGCAGTGAT  
TGATCCTAAGTACTCTGAATATTGACATTTTAACTAATTTGATGGCTAGGTCCTCATTATATTAGTTTAT  
TGCCATCTCTTTGTAGACATCAAAGCAGCAAAAAAGGAA

The following amino acid sequence <SEQ ID NO. 244> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 116:

IFYLRNFFQLHNLLLEMSSEFLDCCLNSFVRAPITKYHRLGLDLYNMNLFSQLILESGCSSRRCQVWFLLRPL  
SLAHRRTSSCCVFTWLSLCVCLCPNLLFLGHLLCSIRAHLNDLSILTALRYFLQIQTHFKVLRRRFNFNMNF  
RGDTNQLITQCYVHNKFNKTCKNIFQILSYNFPICAVIDPKYSELLTFLIWLGPYISLLPSLCRHQSSKKG

The following DNA sequence Seq-2576 <SEQ ID NO. 117> was identified in *H. sapiens*:

GCCTTCCCCCAGTCCCTGTCACAATGGATGGTGCTCAAAAACACGTGTATTGAATGCATTCTTTGAGTCA  
GTGGTTGAATGCCTCTCACACCAGAGGGTGAGGTCTTGAAGGGAGGAACTGCAGTTGGTAGGCTCTGGGT  
CAAGGAGACCTGGATTCAAGTCCTGCCTCTCTAACTTACTGGCTTTGGGCAAATTACTTAACTGGCTGAG  
CCTTGGTTTCTCATCTGTGAAATGCAGTTGCTGTGAGGATTTGATGAGCCAATGCACATGAGACTTGGAGG  
AGTACTGGCTGTGAATGCAAGGGTTGCCCTTGGTGCTCTCTTCTCATCCCTGGAGCCTGGCCAGTGTGAGG  
GCTGGGAGGATGCAGGTGCTTGAAGATGGGCTTGGCTAATGGGAGTCGCTGTGGCTTTTGCAGATGAATA  
TGAATGCCAGGCTGCCGAATAACGAGTGGTCTACCAGAGTGAGACCTCCTGCTTCAAGCGGCAGCTGG  
TCTTCTTGAATGGCATGAGGCACCCACCATCGCTGTGGCCCTGCTGGCCGCCCTGGGCTTCTCAGCACC  
CTGGCCATCCTGGTGATATTCTGGAGGCACTTCCAGACACCCATAGTTCGCTCGGCTGGGGGCCCATGTG  
CTTCTGATGCTGACACTGCTGCTGGTGGCATAATGGTGGTCCCGGTGTACGTGGGG

The following amino acid sequence <SEQ ID NO. 245> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 117:

PSPQSLSQWMVLKNTCIECILVSGMPLTPEGEVLEGRNCSWALGQGDLDSSPASLTYWLWANYLTWLSLGF  
LICEMQLLGFDPEMHMRLEEYWLMQGLPLVLSLHPWSLALCRAGRMQVLGRWAWLMGVAVAFADYEYCQAC  
PNNEWSYQSETSCFKRQLVFLEWHEAPTIAVALLAALGFLSTLAILVIFWRHFQTPIVRSAGGPMCFLMLT  
LLLVAYMVPVYVG

The following DNA sequence Seq-2577 <SEQ ID NO. 118> was identified in *H. sapiens*:

ATGTGTATATATATATAAAAAAGGTAATATAAAATATATGTAATATAAATATATGTAATATTTAATATA  
CATAAATGTATGTAATATATAAAATATATAAAATATATGTAATATAAATATATGTAATATTTTATAC  
TATAAATATATATAAATGCAGGGGTTTAAATCATATTTATATGATATATATGTAATATATATATGTG  
TGTGTGTATATATACATATATGATTTTAAACCCTGCATTTTTTATATTATTGGAGTAGAACCAATCCT  
TTTGTGTGTAATAAAGCTAGCCACGGATACATTTGCCTAGATTTTTGATTTATTGTTGAGCTGCCAAG  
GATGGCAACAACTTCAAGACTTTCTTTGGCAATAAAACATAGTCAACATATTTAAATAAACAACATTTAA  
ATAAATATACCGTAAAGTATAATTAACATTCTTTAAATGAAAACACTTGATTAAATATTTCTAAATG  
GAGTATCAAGATTTTGATACTTATAAGAGATTATGGTGTCTGTGAAAGAATTGATAAATAGATCAATAGAA

GTCAAGAAAGTGGTTACTTTTGGAGAAGGGATACAGTGGGGATTTTGATTGCTACCAATGTCCAATTTCTT  
GACCCTGTGTGATAGTAAATCATTTGACTCTACA

The following amino acid sequence <SEQ ID NO. 246> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 118:

VESNDVLLSHRVKKLDIGSNQNPHCIPSPKVTTFLTSIDLFINSFDTTIISYKYQNLDTPFRNNFNQVFSF  
RMFNYTLRYIYLNVCIFYVDYVLLPKVKVLLPSLAHKIKKSRQMPWLAFSYQQKDWFYSSNNIKNAGF  
NHICIYTHTHIYDFTYISYKYDFKPLHLIYIFYKYIYFIYFIYFIYILHTFYVYLIFYIYLYIYFIY  
PFLYIYTH

The following DNA sequence Seq-2578 SEQ ID NO. 119> was identified in *H. sapiens*:

CACACACCTTCTTCGTGTCTGAACCCTGCAAAAACATTCATAAACTATTAGATTTAGATAACATATTT  
CAAATAGGTTTATTCTTTAATTCAATTCATATTTACTGAATACTATTTGCCAAAAACAGTGGTAAATACTG  
AAGATATAAAGATGAGTAAGTTCTTGTACTCAAGAAGCTTATGGTCTAGTAAAAAAAATGCAGTCATG  
CAAACAAATAAAGACAAAAGGATATCAAATGTGAAACAATACATACAGAGCTTTACACAGAAATATGTAGT  
CATTACAAGGAGAGTTGGAAAATGCTTTAAACAAGGTAATAGCTGATCTGAGTTTGGAAAGCTGAGCAGC  
TCTTTAGCAAGAAAGCAAGCATAATAGATGACTCAAAAGCCAAAATGTTACTATCCGAGTGACATGGATTG  
CTGTTATAAGATAGGTAGTAATCTAAAAATTGTGTTTATGTGTGTCTAAAATATGTCTCTGCGTTGCACT

The following amino acid sequence <SEQ ID NO. 247> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 119:

VQRRDIFTHINTIFRFYLSYNSNPCHSDSNILAFESSIMLAFLKTCFAFKTQISYYVLVKHFEPTLLVMTT  
YFCVKLCMYCFDILLSLFVCMATAFFFLDHKLEYKNLLIFISSVFTTVFGKYSVNMNIKETYLYKYVII  
FYECFLQGSDDNEEGV

The following DNA sequence Seq-2579 <SEQ ID NO. 120> was identified in *H. sapiens*:

CTCCTGGAGCCTGGACTCACATACATCACCATGACTGAGCCATAGAAGAAAGAAACAACCAAGAAATGGGA  
AGCACATGTAGAGAAAGCTTTGTTCTGCCTGAGCCAGCTGGGACCCACAGAACAGCTCGCAAAACTAAGA  
TATGGGACCCAAAGATGTAGAGGAAGGTGATGAAGATGATGAGAGAGCTTACTGTAGCACAAAGTCAGAGTA  
GTTTTGGGAACTGGGGCACAGGACAGTGCCAGCAATGGTCCCAGGTTACAGAAAAATGGTCAGTGATGTT  
AGGGCCACAGAAAGGCACTCGGGACATAAGCACTGCAGGCATCAGTATGGATAGAAAACCACTGCCCTGC  
AGAAGGCCACTAATCGGACACACAGGTGGTGAGTCATGACTGTGGGATAATGCAAAGGTCGACAGATGGTA  
AGGAACCGATCAAAGGACATCACAGACAGAAAGTAGCCTTCTGCAGCACACATGGAGAAGTAGAAGAAGCTG  
GAGCAGGCAGCCAGCATAGGAGATGCTCTTGATATGGGAGATGAGATTGGCCAACATTTTGGGACATCAGA  
ACTAATGCAGCAGATCTCCAGGAAAGAGAAATTAGCCAAGAGGATGTACATAGGTGTGTGGAGTTTCTGGC  
TTGACCACACAGCGCAGATGATGGATGTGTTACCCA

The following amino acid sequence <SEQ ID NO. 248> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 120:

GHIHHLRCVVKPETPHTYVHPLGFLFPGDLLHFPCPKMLANLISHIKSISYAGCLLQFFYFSMCAAEYFLS  
VMSFDRFLTICRPLHYPTVMTHLVCVRLVAFCRAGGFLSILMPAVLMSRVFPCGPNITDHFNCNLGPLLAL  
SCAPVPKTTLTCAVSSLIIFITFLYILGSHILVLRVLWVPAGSGRNKAFSTCASHEFLVVSFFYGSVMVM  
YVSPGSR

The following DNA sequence Seq-2580 <SEQ ID NO. 121> was identified in *H. sapiens*:

GTGTGACCTTGGGCGTGTACATGACTTCCTGAACTGTGCTGTTGTCTGTAAAGGGAGGTGGTCAGACTGG  
GATCCTCTCCAGGATTGCAGGCCTGTCTTATTATCTTGTGTTTACTTCAGTCTGCCAGGATTTCTTTCTGGA  
ACTCCCTGTGGTCCCAGTTGCCGATTTTCAAGATTGCTGTGGGGAATGCCATGGAATAGAATCTGGCCAC  
CTTGAGCTGAGAAAGGTGTTTGTGATTGATGGTTGATGCCACCAAGCAAACAGGGTTAAGCAAACTTGACTG  
CCTGCCTGCTGCTTTTAAAAAGGCAGCTGACGACCTAATCTGTTTAGAATTAGGGGCGAAGCTAAGGAAA  
CTGGCTCAGGCTGTGAGTATCATCTCTAGATTGAGATTTCTGGGACCACATCAGAAACCAGGTTTATGTG  
GACCTTTGATGGGCAGTGTGGTGTGCAACGTGGGGGACTGTGGGTTTTAGACTGGGCAGTTCTGGCTGGGG  
ATTCCAGTTCTACCCCTTAGCAGCATTGTTGGGAGGACGAAAGGGAAATGCCGATGGGAAGTGCAAGATG  
CAGC

The following amino acid sequence <SEQ ID NO. 249> is the predicted

amino acid sequence derived from the DNA sequence of SEQ ID NO. 121:

AASCTSHPAFPFRPPNNAAGNWNQPELPSLKPTVPHVAHHTAHQRSTNLVSDVVPEIIRYSQPEPVSLA  
SPLILNRIRSSAAFLKAAGRQSSCLTLFAWWHQPSITNTFLSSRWPDSPWHSPQQSLKSGNWDHREFQKE  
ILADSKTRDRPAILERIPVPPFFTDNSTVQEVMAHQGH

The following DNA sequence Seq-2581 <SEQ ID NO. 122> was identified in *H. sapiens*:

TCTAAAATATTCAAACCATGACATTTGTGAATTTTCTATGAAAAAAGAGGGAAGTTAGCTCGTTATTTCAG  
ATGATAAAAGCCTCTTCCTTCTCTATTTTCCATTTCACCATCACACCAGGGGAAATTATGGAGATGAGA  
AATACTACCCAGACTTTATTCTCCTGGGACTCTTTAACCACACCAGAGCCCAAGTCCTCTTCATGAT  
GGTCTGAGTATCGTTTTGACCTCCCTGTTTGGCAATTCCTCATGATTCTCCTGATTACCGGGACCGGC  
CGGCTCCACACGCCCATTGACTTCTCCTGAGCCAACCTCTCCCTCATGGACGTGATGCTGGTTTCCACCAC  
TGTGCCCAAAATGGCGGCTGACTACTTGACCGGAAATAAGGCCATCTCCGCGCTGGCTGTGGTGTGCAGA  
TCTTCTTCTGCTCACCTGGGTGGTGGAGAGTGCTTCTCTTAGCAGCCATGGCCTATGACCGCTATGCG  
GCTGTCTGCCACCCACTCCGATATCCACTCTCATGAGCTGGCAGCTGTGCCTGAGGATGACCATGTCTGTC  
CTGGCTCCTGGGTGCAGCTGACGGGCTCCTGC

The following amino acid sequence <SEQ ID NO. 250> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 122:

LKYSNHDICEFSMKRGLARYSDDKSLFLLYFSICTITPGEIMEMRNTTPDFILLGLFNHTRAHQVLFM  
MVLISIVLTSFLGNSLMILLIHRD

The following amino acid sequence <SEQ ID NO. 251> is a predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 122:

RLHTPMYFLLSQLSLMDVMLVSTTVPKMAADYLTGNKAISRAGCGVQIFFLLTLGGGECFLAAMAYDRYA  
AVCHPLRYPTLMSWQLCLRMTMSSWLLGAADGLL

The following DNA sequence Seq-2582 <SEQ ID NO. 123> was identified in *H. sapiens*:

TTCCAGCTCTACCACTAGCCTGCTGGGCGTGTTCTGCAAACCTCTCTCCCTCCCTGGGCCTCAGTTTTTG  
TATTTGCAAAATGGCAGTGGGTGAGACCCCTTAGCCTCAAAGGGCCCTCCCAACCTCTGGCACTTGAGCAT  
CTCTGAGCCTGCTGGGCCACCTGTCCAGTGCCTCTTGGGCTTTGGAAGTTGAATGCTGCAACCCCAAGCC  
CCAGTTTCAGGTAGGGATGAGCCCATTCGCCAATGCTGGGGTCCGAGTGGGCCTGAAGGCTCCAGAGGAC  
CAGTTCTCAGCCTGGATGGGCAGGACCTGGAGACCTGGCCTGTGTGGACACAGGGGAGTAAGTACTG  
GGACTGAGCCTGTAGTTTTGCTTCTTCCACCCCAACCCGTTGGGGGTCGTTCTCACAGCTTGGTGTGGGTA  
CACCAGGGGACTCACCATTGGAGGGATCCGATGGGTTCCAAGGTGCACAAAACAGACCCCCAGGTCATCCT  
CAGGTGGTCTACACAGCCTGTGGCTAAAGCAACTGCTGTCTCCAGCACTTCTTAGCTTCAGTCTGGTAAA  
GGAAGAAAGTCCCCTTGGCAGTGTCTTACAGGCAGTCATAGAGGGACCCACAGCCTGGCCAAAATGCTCA  
ATTTAGAAAATCCCAGACTCAT

The following amino acid sequence <SEQ ID NO. 252> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 123:

MSLGFSEIEHFGQAVGSLYDCLDTAKGTFFLSPDSEVLETAVALATGCVDLRMTWGSVLCTLEPIGSLQW  
VPWCTQHQAVRTTPNGLGGRSKTTGSPVLTPLCPHRPGLQGPCPSRAENVVLWEPSPGLPQHWAMGSSL  
PETGAWGCSIQLPKPKRHWDRWPSRLRDAQVPEVGRALGGVPTAILQIQKLPRERGERFAEHAQQASGRAG

The following DNA sequence Seq-2583 <SEQ ID NO. 124> was identified in *H. sapiens*:

TAGGTGGTGAAGCTGAATCAATCTTCACTAAGGTGTCAGGTGCTCAGGCTAAACCTGCAGCTTTCCAAT  
AGGGAAAACATTTCAGTCTAGTAGCTTGTCTGCTACTAGACTGCCTCAGTGAATGAGTAAGTACTGGATT  
AAACAAAACACCCCAAGAAATATTTACCAAGAAGGTAAGGTCCAAAAGGAAGGTAGTGAAGGAAATGTACT  
CTGATCATGAAATGGTTGGTTGATGAGCAAGTCAAGCTTGAAGATTATCTCTTTTCTTCACTCAGAAAAG  
CAACTGAAATGCAAACTGGTGCTATTAATAACATAGTCCTTGAAGACAACCTAAAAATAGTTCCTAAAAATG  
CCATTGTAACTGTAATTTTGCATCTCAATCATTGGCAGTTTGGAAATGACAGTATTTTGTACAGCAAGATG  
ATGCACATTATAATACTATATATAGAGAGAGAGATGCATGTGCTCCTCCTTCTTCCCCACACAATCAC  
CCGGAGGTCTAAAAATGTTTAAAGTCCACCAGGAGTAAGCAAAAATTTAACAAGGAAATACATACTCATT  
TTACATTTAGGTAATTAAGTAGTAATCTCCTTGATGTTAATTTTATTCTCCAAGTTAAAGTCTTGCTT



ATATGAACTCTTGCTTTCTAA

The following amino acid sequence <SEQ ID NO. 253> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 124:

RWAESIFITKVSGAQAKPAAFQGKHSVLVLLDCLSEVTDWIKQNTPEIFTKKVRSKRKVVKGNVLSNGWL  
MSKSSLKIYLFSSFRKATEMQTGAINNIVLEDNLKIVPKMPFVTVILHLNHWQFGMTVFCTARCTLYIYIRE  
RHACAPFPSSPHKSPGGHKNVVPPGVSKNLTRKYILILHLGNVVISLMLIFISPPSSSCLYELLS

The following DNA sequence Seq-2584 <SEQ ID NO. 125> was identified in *H. sapiens*:

TACCAAGTAAAAATTTTAAAGCCGATTATTTTATTTCTGCTTTCATGAATTTCCAGTGTAATGGAGAAGAT  
AAGAGGAAATAAGTAAGCATGTATCTGGCCAATTACTTATATGTTTTATAGAGTTACAGACATAATTATAA  
ATCAGGTAGGTTAGGGAGATACAAGTTTCATTTAAGAAATGAAGTGTAGGGGAAGGTAGTGGGGAAGAGGG  
ATCAGGAGAGGTTGGCCAATGGGTACAAAGTTACAGTTAGGAAGAATAAGTCTGGTGTTTTGTGTACAG  
TAGGGTGCTCTGGCAAACAACAATGTAGTGTATACTTTTAAAGATAGCTAGAAGAGAAGATTTTGAATGTT  
ATCACCATAAGAAATGATCAATGTTTAAAGTAGTAAATACAGTAATGACCATGATTTGATCATCATGCAA  
TGTATACACTCATTGAAACATCACACTGTACCCCATAAATGTGTACAATCATTATGTCAATTATAAATATT  
AAAAATTAATTTTAAAGAAGAACGCAGAAAAAAATGTTAACAGTGTCTAAAGGAAGGGACAGTTGCATCG  
GAAAGACTTGGAAATGTGTAAGGTGACAGTCAAGAGAAATGGGAGTTTATGGTGACCGAGTAGGATATGGA  
TCAAGGTAACCAACAGCAATGGGTGTGAAGCATTGCATATG

The following amino acid sequence <SEQ ID NO. 254> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 125:

YAMLHHCWWLPSISYSVTINSHFSLSPYTFPSLSDATVPSFRTLLTFFSAFLLKINFYLLTLYTFMGYSV  
MFQVYTLHDDQIMVITVFTTLNIDHFLVVITFKIFSSSYLKSIIHYIVVCQRHPTVQONRTYSSLLCTHWP  
TSPDPSSPLPSPTVHFLNETCISLTYLIYNYVCNSIKHISNWPDTCLLISSYLLHYTGNSKQKNRNLNFYL  
V

The following DNA sequence Seq-2585 <SEQ ID NO. 126> was identified in *H. sapiens*:

GGCTGCGTGCATCATTTCCCTTGTACAGCTGGACAGGGAAACGCGGTTGTGCTCTGGCTCCTGGGCTTCCG  
CATGCGCAGGGAACGCCGTCTCCATCTACATCCTCAACCTGGCTGCGGCAGACTTCCTCTTCCCTCAGCGGC  
CACGTTATACGTTCCGCCTCACTCCTCATCAATATCTGTCTATCCCATCTCCAAAATCCTCATTCTGTGAT  
GACCTTTCTATCTTTACAGGCCTGAGCTTCTGAGTGCCATGAGCACCGAGCGCTGCCTGTGCGTCTCTGT  
GGCCCATCTGGTACCGCTGCCTCCTCCCCCACACACCTGTACGCGGTGCTGTGTGCTTGTGCTTTGGGCCC  
TGTCCCTACTGCGGAGCATCCTGGAGTGAATGTTCTGTGACTTCCTGTTTAGTGATGCTGATTCTATTTGG  
TGTCAACCATCAGATTTTCATCACAGTCGTGTGGCTGATTTTTTATGTGTGGTCTCTGTGGGTCCAGCCT  
GGTCTGCTGATTAGGATTCTCTGTGGATCCTGGAAGATGCCTCTGACCGGGCTGTACGTGACGATCCTGC  
TCACAGTGCTAGTCTTCTACTCCGCAGCCTGCCCTTCGGCATTCCGTGGGCTCTGTCTACTGGGATACAC  
CTG

The following amino acid sequence <SEQ ID NO. 255> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 126:

AACIIISLVTLDRTRLCSGSWASACAGNAVSIYIILNAAADFLFLSGHVIRASALLINICHPIISKILIPVM  
TFLYFTGLSFLSAMSTERCLCVLWPIWYRCLLPHTCQRSCVSCFGPCPYCGASWSECSVTSLVMLILFG  
VNHQISSQSCGFFYVWFSVGPWASCLGFSVDPGRCLPGCTRSCSQCSSYSAACPSAFGGLCLLGYT

The following DNA sequence Seq-2586 <SEQ ID NO. 127> was identified in *H. sapiens*:

AACAAAACAACTCCTGTTATTCCGAAGGAGAAAAGAAACATTTTCTGTTTTAATTTGTGATCATCAGGGTC  
TTCTAAAGCATAGGGCTCAGGGAAGGAGGGTTATCAACATCTGGCCAAGGGCTGGAGATGGAAATGTTTCC  
AGACCCTAAAGCAAGAAAAAGATCAGCAGGTTAGAGAAAAAGTAAGATGGCCACTTACTTAGAGTGAATTT  
AGATAAGAATAAAAGCCGTGCCCCAGGAGTAGGCAAGAGGCTGATTATTGAGATCCTGTAACCCATGGGAA  
GGAACCCCTAATCTTATGATGCTGGTGATGAGAAAGTGTGGTGGGGTAGAGTAAGAGAACACATTAATCTG  
CTTTGCCTCATGGAAAGAATAAATCTGGTAGACATATGTAGATGCAGAGAGTGAGCTATTATAGTTTTTG  
TAAGAGAGATTATGGTTTGACTTATGGTGACAGTGATGGACATGGTGAGCAATGGATGCCTTTGTGATCTG  
CAGACTTTTACCTGACACACTGAGTGCATGATCATGCCATTTACTGAGAGGTGACAATGG

The following amino acid sequence <SEQ ID NO. 256> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 127:

PLSPLSKWHHDHALSVSGKKSADHKGIHCSPCPSLSPVKPSLLQKLLTLCIYICLPEFILSMRQSRMLMCSLT  
LPHQHFLITSIIIRLGFLPMGYRISIIISLLPTPGARLLFLSKFTLSKWPSYFFSNLLIFFLLGLETFPSPAL  
GQMLITLLPALCFRRPSQIKTENVSFLLRNRRSCFV

The following DNA sequence Seq-2587 <SEQ ID NO. 128> was identified in *H. sapiens*:

CTTTGGGCTCTGATAAATTTTTTTCTGATTTTTTGCAGGGAACACATTTGAAATAATAGGACTGAAAAT  
TATGAGGAAGAAACATTTGTCCTTGGTGTCTGAAATATGTGAACCAACCCCAATGCCTGCACTTTTGC  
TCTCACAACCTTCTGACATGAGGCACAGATTTTACAAAACAGCTTAACATAGAAGTCTCACAAAATGTGC  
AGATTTCTCAGATCCCAAAAACAATGGAAAAGCACTCAGACCACAAGAGCTTCATGGGAATAGCAGAAAG  
AAGAGGCGAACTTTGGCTGTCACTGTGAATGCCCTGGAATGTTAGTGGATGAACAGAGAAGCCTTAGAAGA  
TTTAAGAGCATAATAAGCATAGGTTAGGAAATTTCCACCTGTGGCAGCAAAAGAAGTAAATTTAGAAATTT  
CCAGAACCAATTTCTTTGAAGCAGAACTTCCAACACCACATTTTAAAGGTTTTTCTCCTTGGCCTTTGCAC  
CTCTCATCTTTGTTATTTGTTTCTTCCCTATTGGGCTGTTGCCTATTATTGTCTCTCTTTTACATTC  
CAAAGAACATTTCTTTACTGTAGGACA

The following amino acid sequence <SEQ ID NO. 257> is the predicted amino acid sequence derived from the DNA sequence of SEQ ID NO. 128:

LWALINFFSDFEAGNTFEIIGLKIMRKKHLSLVFLKYVNQTPMPALLLSQTSMDMRHRLQNSLTKSHKMCR  
FPQIPKTMKHS DHKSFMGIAERRGELWLSLMPWNVSGTEKPKIEHNKHRVGNFHLWQQKINFPEPISLK  
QNFQHHIFKVFLGLCTSHLCYLFILPYWAVAYYCLSFYIPKNISFTVG

## EXAMPLE 2: CLONING OF nGPCR-x

[000239] cDNAs may be sequenced directly using an ABI377 or ABI373A fluorescence-based sequencer (Perkin Elmer/Applied Biosystems Division, PE/ABD, Foster City, CA) and the ABI PRISM Ready Dye-Deoxy Terminator kit with Taq FS polymerase. Each ABI cycle sequencing reaction contains about 0.5µg of plasmid DNA. Cycle-sequencing is performed using an initial denaturation at 98°C for 1 min, followed by 50 cycles: 98°C for 30 sec, annealing at 50°C for 30 sec, and extension at 60°C for 4 min. Temperature cycles and times are controlled by a Perkin-Elmer 9600 thermocycler. Extension products are purified using Centriflex gel filtration (Advanced Genetic Technologies Corp., Gaithersburg, MD). Each reaction product is loaded by pipette onto the column, which is then centrifuged in a swinging bucket centrifuge (Sorvall model RT6000B table top centrifuge) at 1500 x g for 4 min at room temperature. Column-purified samples are dried under vacuum for about 40 min and then dissolved in 5µl of a DNA loading solution (83% deionized formamide, 8.3 mM EDTA, and 1.6 mg/ml Blue Dextran). The samples are then heated to 90°C for three min and loaded into the gel sample wells for sequence analysis by the ABI377 sequencer. Sequence analysis is performed by importing ABI373A files into the Sequencer program (Gene Codes, Ann Arbor, MI). Generally, sequence reads of 700 bp are obtained. Potential sequencing errors are minimized by obtaining sequence information from both DNA strands and by re-sequencing difficult areas using primers at different locations until all sequencing ambiguities are removed.

- [000240] To isolate a cDNA clone encoding full length nGPCR, a DNA fragment corresponding to a nucleotide sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128, or a portion thereof, can be used as a probe for hybridization screening of a phage cDNA library. The DNA fragment is amplified by the polymerase chain reaction (PCR) method. The PCR reaction mixture of 50 $\mu$ l contains polymerase mixture (0.2mM dNTPs, 1x PCR Buffer and 0.75 $\mu$ l Expand High Fidelity Polymerase (Roche Biochemicals)), 1 $\mu$ g of 3206491 plasmid, and 50pmoles of forward primer and 50pmoles of reverse primer. The primers are preferably 10 to 25 nucleotides in length and are determined by procedures well known to those skilled in the art. Amplification is performed in an Applied Biosystems PE2400 thermocycler, using the following program: 95°C for 15 seconds, 52°C for 30 seconds and 72°C for 90 seconds; repeated for 25 cycles. The amplified product is separated from the plasmid by agarose gel electrophoresis, and purified by Qiaquick gel extraction kit (Qiagen).
- [000241] A lambda phage library containing cDNAs cloned into lambda ZAPII phage-vector is plated with E. coli XL-1 blue host, on 15 cm LB-agar plates at a density of 50,000 pfu per plate, and grown overnight at 37°C; (plated as described by Sambrook *et al.*, *supra*). Phage plaques are transferred to nylon membranes (Amersham Hybond NJ), denatured for 2 minutes in denaturation solution (0.5 M NaOH, 1.5 M NaCl), renatured for 5 minutes in renaturation solution (1 M Tris pH 7.5, 1.5 M NaCl), and washed briefly in 2xSSC (20x SSC: 3 M NaCl, 0.3 M Na-citrate). Filter membranes are dried and incubated at 80°C for 120 minutes to crosslink the phage DNA to the membranes.
- [000242] The membranes are hybridized with a DNA probe prepared as described above. A DNA fragment (25ng) is labeled with  $\alpha$ -<sup>32</sup>P-dCTP (NEN) using Rediprime random priming (Amersham Pharmacia Biotech), according to the manufacturer's instructions. Labeled DNA is separated from unincorporated nucleotides by S200 spin columns (Amersham Pharmacia Biotech), denatured at 95°C for 5 minutes and kept on ice. The DNA-containing membranes (above) are pre-hybridized in 50ml ExpressHyb (Clontech) solution at 68°C for 90 minutes. Subsequently, the labeled DNA probe is added to the hybridization solution, and the probe is left to hybridize to the membranes at 68°C for 70 minutes. The membranes are washed five times in 2x SSC, 0.1% SDS at 42°C for 5 minutes each, and finally washed 30 minutes in 0.1x SSC, 0.2% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with an intensifying screen at -80°C for 16 hours. One positive colony is isolated from the plates, and re-plated with about 1000 pfu on a 15 cm LB plate. Plating, plaque lift to filters and hybridization are performed as described above. About four positive phage plaques are isolated from this secondary screening.

[000243] cDNA containing plasmids (pBluescript SK-) are rescued from the isolated phages by in vivo excision by culturing XL-1 blue cells co-infected with the isolated phages and with the Excision helper phage, as described by the manufacturer (Stratagene). XL-blue cells containing the plasmids are plated on LB plates and grown at 37°C for 16 hours. Colonies (18) from each plate are replated on LB plates and grown. One colony from each plate is stricken onto a nylon filter in an ordered array, and the filter is placed on a LB plate to raise the colonies. The filter is then hybridized with a labeled probe as described above. About three positive colonies are selected and grown up in LB medium. Plasmid DNA is isolated from the three clones by Qiagen Midi Kit (Qiagen) according to the manufacturer's instructions. The size of the insert is determined by digesting the plasmid with the restriction enzymes NotI and SalI, which establishes an insert size. The sequence of the entire insert is determined by automated sequencing on both strands of the plasmids.

### EXAMPLE 3: SUBCLONING OF THE CODING REGION OF nGPCR-X VIA PCR

[000244] Additional experiments may be conducted to subclone the coding region of nGPCR and place the isolated coding region into a useful vector. Two additional PCR primers are designed based on the coding region of nGPCR, corresponding to either end. To protect against exonucleolytic attack during subsequent exposure to enzymes, *e.g.*, Taq polymerase, primers are routinely synthesized with a protective run of nucleotides at the 5' end that were not necessarily complementary to the desired target.

[000245] PCR is performed in a 50µl reaction containing 34µl H<sub>2</sub>O, 5 µl 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5µl 15mM MgSO<sub>4</sub>, 2µl dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10 mM), 3µl genomic phage DNA (0.25µg/µl), 0.3µl Primer 1 (1µg/µl), 0.3µl Primer 2 (1µg/µl), 0.4µl High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction was started with 1 cycle of 94°C for 2 minutes; followed by 25 cycles at 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for 1.3 minutes.

[000246] The contents from the PCR reaction are loaded onto a 2% agarose gel and fractionated. The DNA band of expected size is excised from the gel, placed in a GenElute Agarose spin column (Supelco) and spun for 10 minutes at maximum speed in a microfuge. The eluted DNA is precipitated with ethanol and resuspended in 6µl H<sub>2</sub>O for ligation.

[000247] The PCR-amplified DNA fragment containing the coding region is cloned into pCR2.1 using a protocol standard in the art. In particular, the ligation reaction consists of 6µl of GPCR DNA, 1µl 10X ligation buffer, 2µl pCR2.1 (25ng/µl, Invitrogen), and 1µl T4 DNA ligase (Invitrogen). The reaction mixture is incubated overnight at 14°C and the reaction is then stopped by heating at 65°C for 10 minutes. Two microliters of the ligation reaction are

transformed into One Shot cells (Invitrogen) and plated onto ampicillin plates. A single colony containing a recombinant pCR2.1 bearing an insert is used to inoculate a 5ml culture of LB medium. Plasmid DNA is purified using the Concert Rapid Plasmid Miniprep System (GibcoBRL) and sequenced. Following confirmation of the sequence, a 50 ml culture of LB medium is inoculated with the transformed One Shot cells, cultured, and processed using a Qiagen Plasmid Midi Kit to yield purified pCR-GPCR.

#### **EXAMPLE 4: HYBRIDIZATION ANALYSIS TO DEMONSTRATE nGPCR-X EXPRESSION IN BRAIN**

[000248] The expression of nGPCR-x in mammals, such as the rat, may be investigated by *in situ* hybridization histochemistry. To investigate expression in the brain, for example, coronal and sagittal rat brain cryosections (20µm thick) are prepared using a Reichert-Jung cryostat. Individual sections are thaw-mounted onto silanized, nuclease-free slides (CEL Associates, Inc., Houston, TX), and stored at -80°C. Sections are processed starting with post-fixation in cold 4% paraformaldehyde, rinsed in cold phosphate-buffered saline (PBS), acetylated using acetic anhydride in triethanolamine buffer, and dehydrated through a series of alcohol washes in 70%, 95%, and 100% alcohol at room temperature. Subsequently, sections are delipidated in chloroform, followed by rehydration through successive exposure to 100% and 95% alcohol at room temperature. Microscope slides containing processed cryosections are allowed to air dry prior to hybridization. Other tissues may be assayed in a similar fashion.

[000249] A nGPCR-x-specific probe is generated using PCR. Following PCR amplification, the fragment is digested with restriction enzymes and cloned into pBluescript II cleaved with the same enzymes. For production of a probe specific for the sense strand of nGPCR-x, the nGPCR-x clone in pBluescript II is linearized with a suitable restriction enzyme, which provides a substrate for labeled run-off transcripts (*i.e.*, cRNA riboprobes) using the vector-borne T7 promoter and commercially available T7 RNA polymerase. A probe specific for the antisense strand of nGPCR-x is also readily prepared using the nGPCR-x clone in pBluescript II by cleaving the recombinant plasmid with a suitable restriction enzyme to generate a linearized substrate for the production of labeled run-off cRNA transcripts using the T3 promoter and cognate polymerase. The riboprobes are labeled with [<sup>35</sup>S]-UTP to yield a specific activity of about 0.40 x 10<sup>6</sup> cpm/pmol for antisense riboprobes and about 0.65 x 10<sup>6</sup> cpm/pmol for sense-strand riboprobes. Each riboprobe is subsequently denatured and added (2 pmol/ml) to hybridization buffer which contained 50% formamide, 10% dextran, 0.3 M NaCl, 10 mM Tris (pH 8.0), 1 mM EDTA, 1X Denhardt's Solution, and 10 mM dithiothreitol. Microscope slides containing sequential brain cryosections are independently exposed to 45µl of hybridization

solution per slide and silanized cover slips are placed over the sections being exposed to hybridization solution. Sections are incubated overnight (15-18 hours) at 52°C to allow hybridization to occur. Equivalent series of cryosections are exposed to sense or antisense nGPCR-x-specific cRNA riboprobes.

[000250] Following the hybridization period, coverslips are washed off the slides in 1X SSC, followed by RNase A treatment involving the exposure of slides to 20 µg/ml RNase A in a buffer containing 10mM Tris-HCl (pH 7.4), 0.5M EDTA, and 0.5M NaCl for 45 minutes at 37°C. The cryosections are then subjected to three high-stringency washes in 0.1 X SSC at 52°C for 20 minutes each. Following the series of washes, cryosections are dehydrated by consecutive exposure to 70%, 95%, and 100% ammonium acetate in alcohol, followed by air drying and exposure to Kodak BioMax™ MR-1 film. After 13 days of exposure, the film is developed. Based on these results, slides containing tissue that hybridized, as shown by film autoradiograms, are coated with Kodak NTB-2 nuclear track emulsion and the slides are stored in the dark for 32 days. The slides are then developed and counterstained with hematoxylin. Emulsion-coated sections are analyzed microscopically to determine the specificity of labeling. The signal is determined to be specific if autoradiographic grains (generated by antisense probe hybridization) are clearly associated with cresyl violet-stained cell bodies. Autoradiographic grains found between cell bodies indicates non-specific binding of the probe.

[000251] As discussed above, it is well known that GPCRs are expressed in many different tissues and regions, including in the brain. Expression of nGPCR-x in the brain provides an indication that modulators of nGPCR-x activity have utility for treating neurological disorders, including but not limited to, mental disorder, affective disorders, ADHD/ADD (*i.e.*, Attention Deficit Hyperactivity Disorder/Attention Deficit Disorder), and neural disorders such as Alzheimer's disease, Parkinson's disease, migraine, and senile dementia. Some other diseases for which modulators of nGPCR-x may have utility include depression, anxiety, bipolar disease, epilepsy, neuritis, neurasthenia, neuropathy, neuroses, and the like. Use of nGPCR-x modulators, including nGPCR-x ligands and anti-nGPCR-x antibodies, to treat individuals having such disease states is intended as an aspect of the invention.

#### EXAMPLE 5: TISSUE EXPRESSION PROFILING

[000252] A PCR-based system (RapidScan™ Gene Expression Panel, OriGene Technologies, Rockville, MD) may be used to generate a comprehensive expression profile of the putative nGPCR-x in human tissue, and in human brain regions. The RapidScan Expression Panel is comprised of first-strand cDNAs from various human tissues and brain regions that are serially diluted over a 4-log range and arrayed into a multi-well PCR plate. Human tissues in the array

may include: brain, heart, kidney, spleen, liver, colon, lung, small intestine, muscle, stomach, testis, placenta, salivary gland, thyroid, adrenal gland, pancreas, ovary, uterus, prostate, skin, PBL, bone marrow, fetal brain, and fetal liver.

[000253] Expression of nGPCR-x in various tissues is detected using PCR primers designed based on the available sequence of the receptor that will prime the synthesis of a predetermined size fragment in the presence of the appropriate cDNA.

[000254] PCR is performed in a 50 $\mu$ l reaction containing 34 $\mu$ l H<sub>2</sub>O, 5 $\mu$ l 10X TT buffer (140 mM ammonium sulfate, 0.1% gelatin, 0.6 M Tris-tricine, pH 8.4), 5 $\mu$ l 15mM MgSO<sub>4</sub>, 2 $\mu$ l dNTP mixture (dGTP, dATP, dTTP, and dCTP, each at 10mM), 0.3 $\mu$ l forward primer (1 $\mu$ g/ $\mu$ l), 0.3 $\mu$ l reverse primer (1 $\mu$ g/ $\mu$ l), 0.4 $\mu$ l High Fidelity Taq polymerase (Boehringer Mannheim). The PCR reaction mixture is added to each well of the PCR plate. The plate is placed in a MJ Research PTC100 thermocycler, and is then exposed to the following cycling parameters: Pre-soak 94°C for 3 min; denaturation at 94°C for 30 seconds; annealing at primer 57°C for 45 seconds; extension 72°C for 2 minutes; for 35 cycles. PCR productions are then separated and analyzed by electrophoresis on a 1.2% agarose gel stained with ethidium bromide.

[000255] The 4-log dilution range of cDNA deposited on the plate ensures that the amplification reaction is within the linear range and, hence, facilitates semi-quantitative determination of relative mRNA accumulation in the various tissues or brain regions examined.

#### EXAMPLE 6: NORTHERN BLOT ANALYSIS

[000256] Northern blots are performed to examine the expression of nGPCR-x mRNA. The sense orientation oligonucleotide and the antisense-orientation oligonucleotide, described above, are used as primers to amplify a portion of the GPCR-x cDNA sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128.

[000257] Multiple human tissue northern blots from Clontech (Human II # 7767-1) are hybridized with the probe. Pre-hybridization is carried out at 42 C for 4 hours in 5xSSC, 1X Denhardt's reagent, 0.1% SDS, 50% formamide, 250 mg/ml salmon sperm DNA. Hybridization is performed overnight at 42°C in the same mixture with the addition of about 1.5x10<sup>6</sup> cpm/ml of labeled probe.

[000258] The probe is labeled with  $\alpha$ -<sup>32</sup>P-dCTP by Rediprime™ DNA labeling system (Amersham Pharmacia), purified on Nick Column™ (Amersham Pharmacia) and added to the hybridization solution. The filters are washed several times at 42°C in 0.2x SSC, 0.1% SDS. Filters are exposed to Kodak XAR film (Eastman Kodak Company, Rochester, N.Y., USA) with intensifying screen at -80°C.

## EXAMPLE 7: RECOMBINANT EXPRESSION OF nGPCR-X IN EUKARYOTIC HOST CELLS

### A. Expression of nGPCR-x in Mammalian Cells

[000259] To produce nGPCR-x protein, a nGPCR-x-encoding polynucleotide is expressed in a suitable host cell using a suitable expression vector and standard genetic engineering techniques. For example, the nGPCR-x-encoding sequence described in Example 1 is subcloned into the commercial expression vector pzeoSV2 (Invitrogen, San Diego, CA) and transfected into Chinese Hamster Ovary (CHO) cells using the transfection reagent FuGENE6™ (Boehringer-Mannheim) and the transfection protocol provided in the product insert. Other eukaryotic cell lines, including human embryonic kidney (HEK-293) and COS cells, are suitable as well. Cells stably expressing nGPCR-x are selected by growth in the presence of 100µg/ml zeocin (Stratagene, LaJolla, CA). Optionally, nGPCR-x may be purified from the cells using standard chromatographic techniques. To facilitate purification, antisera is raised against one or more synthetic peptide sequences that correspond to portions of the nGPCR-x amino acid sequence, and the antisera is used to affinity purify nGPCR-x. The nGPCR-x also may be expressed in-frame with a tag sequence (e.g., polyhistidine, hemagglutinin, FLAG) to facilitate purification. Moreover, it will be appreciated that many of the uses for nGPCR-x polypeptides, such as assays described below, do not require purification of nGPCR-x from the host cell.

### B. Expression of nGPCR-x in HEK-293 cells

[000260] For expression of nGPCR-x in mammalian cells HEK293 (transformed human, primary embryonic kidney cells), a plasmid bearing the relevant nGPCR-x coding sequence is prepared, using vector pSecTag2A (Invitrogen). Vector pSecTag2A contains the murine IgK chain leader sequence for secretion, the c-myc epitope for detection of the recombinant protein with the anti-myc antibody, a C-terminal polyhistidine for purification with nickel chelate chromatography, and a Zeocin resistant gene for selection of stable transfectants. The forward primer for amplification of this GPCR cDNA is determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce the *HindIII* cloning site and nucleotides matching the GPCR sequence. The reverse primer is also determined by routine procedures and preferably contains a 5' extension of nucleotides to introduce an *XhoI* restriction site for cloning and nucleotides corresponding to the reverse complement of the nGPCR-x sequence. The PCR conditions are 55°C as the annealing temperature. The PCR product is gel purified and cloned into the *HindIII-XhoI* sites of the vector.

[000261] The DNA is purified using Qiagen chromatography columns and transfected into HEK-293 cells using DOTAP™ transfection media (Boehringer Mannheim, Indianapolis, IN). Transiently transfected cells are tested for expression after 24 hours of transfection, using



western blots probed with anti-His and anti-nGPCR-x peptide antibodies. Permanently transfected cells are selected with Zeocin and propagated. Production of the recombinant protein is detected from both cells and media by western blots probed with anti-His, anti-Myc or anti-GPCR peptide antibodies.

#### C. Expression of nGPCR-x in COS cells

[000262] For expression of the nGPCR-x in COS7 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 can be cloned into vector p3-CI. This vector is a pUC18-derived plasmid that contains the HCMV (human cytomegalovirus) promoter-intron located upstream from the bGH (bovine growth hormone) polyadenylation sequence and a multiple cloning site. In addition, the plasmid contains the dhfr (dihydrofolate reductase) gene which provides selection in the presence of the drug methotrexane (MTX) for selection of stable transformants.

[000263] The forward primer is determined by routine procedures and preferably contains a 5' extension which introduces an *XbaI* restriction site for cloning, followed by nucleotides which correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128. The reverse primer is also determined by routine procedures and preferably contains 5'- extension of nucleotides which introduces a *SalI* cloning site followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128. The PCR consists of an initial denaturation step of 5 min at 95°C, 30 cycles of 30 sec denaturation at 95°C, 30 sec annealing at 58°C and 30 sec extension at 72°C, followed by 5 min extension at 72°C. The PCR product is gel purified and ligated into the *XbaI* and *SalI* sites of vector p3-CI. This construct is transformed into *E. coli* cells for amplification and DNA purification. The DNA is purified with Qiagen chromatography columns and transfected into COS 7 cells using Lipofectamine™ reagent from BRL, following the manufacturer's protocols. Forty-eight and 72 hours after transfection, the media and the cells are tested for recombinant protein expression.

[000264] nGPCR-x expressed from a COS cell culture can be purified by concentrating the cell-growth media to about 10 mg of protein/ml, and purifying the protein by, for example, chromatography. Purified nGPCR-x is concentrated to 0.5 mg/ml in an Amicon concentrator fitted with a YM-10 membrane and stored at -80°C.

#### D. Expression of nGPCR-x in Insect Cells

[000265] For expression of nGPCR-x in a baculovirus system, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 can be amplified by PCR. The forward primer is determined by routine procedures and preferably contains a 5' extension which adds the *NdeI* cloning site, followed by nucleotides which

correspond to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128. The reverse primer is also determined by routine procedures and preferably contains a 5' extension which introduces the *KpnI* cloning site, followed by nucleotides which correspond to the reverse complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128.

[000266] The PCR product is gel purified, digested with *NdeI* and *KpnI*, and cloned into the corresponding sites of vector pACHTL-A (Pharmingen, San Diego, CA). The pACHTL expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV), and a 6XHis tag upstream from the multiple cloning site. A protein kinase site for phosphorylation and a thrombin site for excision of the recombinant protein precede the multiple cloning site is also present. Of course, many other baculovirus vectors could be used in place of pACHTL-A, such as pAc373, pVL941 and pAcIM1. Other suitable vectors for the expression of GPCR polypeptides can be used, provided that the vector construct includes appropriately located signals for transcription, translation, and trafficking, such as an in-frame AUG and a signal peptide, as required. Such vectors are described in Luckow *et al.*, Virology 170:31-39, among others.

[000267] The virus is grown and isolated using standard baculovirus expression methods, such as those described in Summers *et al.* (A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures, Texas Agricultural Experimental Station Bulletin No. 1555 (1987)).

[000268] In a preferred embodiment, pACHTL-A containing nGPCR-x gene is introduced into baculovirus using the "BaculoGold™" transfection kit (Pharmingen, San Diego, CA) using methods established by the manufacturer. Individual virus isolates are analyzed for protein production by radiolabeling infected cells with <sup>35</sup>S-methionine at 24 hours post infection. Infected cells are harvested at 48 hours post infection, and the labeled proteins are visualized by SDS-PAGE. Viruses exhibiting high expression levels can be isolated and used for scaled up expression.

[000269] For expression of a nGPCR-x polypeptide in a Sf9 cells, a polynucleotide molecule having a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 can be amplified by PCR using the primers and methods described above for baculovirus expression. The nGPCR-x cDNA is cloned into vector pACHTL-A (Pharmingen) for expression in Sf9 insect. The insert is cloned into the *NdeI* and *KpnI* sites, after elimination of an internal *NdeI* site (using the same primers described above for expression in baculovirus). DNA is purified with Qiagen chromatography columns and expressed in Sf9 cells. Preliminary Western blot experiments from non-purified plaques are tested for the presence of the recombinant

protein of the expected size which reacted with the GPCR-specific antibody. These results are confirmed after further purification and expression optimization in HiG5 cells.

#### EXAMPLE 8: INTERACTION TRAP/TWO-HYBRID SYSTEM

[000270] In order to assay for nGPCR-x-interacting proteins, the interaction trap/two-hybrid library screening method can be used. This assay was first described in Fields *et al.*, *Nature*, 1989, 340, 245, which is incorporated herein by reference in its entirety. A protocol is published in Current Protocols in Molecular Biology 1999, John Wiley & Sons, NY, and Ausubel, F. M. *et al.* 1992, Short protocols in molecular biology, Fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety. Kits are available from Clontech, Palo Alto, CA (Matchmaker Two-Hybrid System 3).

[000271] A fusion of the nucleotide sequences encoding all or partial nGPCR-x and the yeast transcription factor GAL4 DNA-binding domain (DNA-BD) is constructed in an appropriate plasmid (*i.e.*, pGBKT7) using standard subcloning techniques. Similarly, a GAL4 active domain (AD) fusion library is constructed in a second plasmid (*i.e.*, pGADT7) from cDNA of potential GPCR-binding proteins (for protocols on forming cDNA libraries, see Sambrook *et al.* 1989, Molecular cloning: a laboratory manual, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY), which is incorporated herein by reference in its entirety. The DNA-BD/nGPCR-x fusion construct is verified by sequencing, and tested for autonomous reporter gene activation and cell toxicity, both of which would prevent a successful two-hybrid analysis. Similar controls are performed with the AD/library fusion construct to ensure expression in host cells and lack of transcriptional activity. Yeast cells are transformed (*ca* 10<sup>5</sup> transformants/mg DNA) with both the nGPCR-x and library fusion plasmids according to standard procedures (Ausubel *et al.*, 1992, Short protocols in molecular biology, fourth edition, Greene and Wiley-interscience, NY, which is incorporated herein by reference in its entirety). *In vivo* binding of DNA-BD/nGPCR-x with AD/library proteins results in transcription of specific yeast plasmid reporter genes (*i.e.*, lacZ, HIS3, ADE2, LEU2). Yeast cells are plated on nutrient-deficient media to screen for expression of reporter genes. Colonies are dually assayed for  $\beta$ -galactosidase activity upon growth in Xgal (5-bromo-4-chloro-3-indolyl- $\beta$ -D-galactoside) supplemented media (filter assay for  $\beta$ -galactosidase activity is described in Breeden *et al.*, Cold Spring Harb. Symp. Quant. Biol., 1985, 50, 643, which is incorporated herein by reference in its entirety). Positive AD-library plasmids are rescued from transformants and reintroduced into the original yeast strain as well as other strains containing unrelated DNA-BD fusion proteins to confirm specific nGPCR-x/library protein interactions. Insert DNA is sequenced to verify the

presence of an open reading frame fused to GAL4 AD and to determine the identity of the nGPCR-x-binding protein.

#### **EXAMPLE 9: MOBILITY SHIFT DNA-BINDING ASSAY USING GEL ELECTROPHORESIS**

[000272] A gel electrophoresis mobility shift assay can rapidly detect specific protein-DNA interactions. Protocols are widely available in such manuals as Sambrook *et al.* 1989, *Molecular cloning: a laboratory manual*, second edition, Cold Spring Harbor Press, Cold Spring Harbor, NY and Ausubel, F. M. *et al.*, 1992, *Short Protocols in Molecular Biology*, fourth edition, Greene and Wiley-interscience, NY, each of which is incorporated herein by reference in its entirety.

[000273] Probe DNA (<300 bp) is obtained from synthetic oligonucleotides, restriction endonuclease fragments, or PCR fragments and end-labeled with <sup>32</sup>P. An aliquot of purified nGPCR-x (*ca.* 15 µg) or crude nGPCR-x extract (*ca.* 15 ng) is incubated at constant temperature (in the range 22-37 C) for at least 30 minutes in 10-15 µl of buffer (*i.e.* TAE or TBE, pH 8.0-8.5) containing radiolabeled probe DNA, nonspecific carrier DNA (*ca.* 1 µg), BSA (300 µg/ml), and 10% (v/v) glycerol. The reaction mixture is then loaded onto a polyacrylamide gel and run at 30-35 mA until good separation of free probe DNA from protein-DNA complexes occurs. The gel is then dried and bands corresponding to free DNA and protein-DNA complexes are detected by autoradiography.

#### **EXAMPLE 10: ANTIBODIES TO nGPCR-X**

[000274] Standard techniques are employed to generate polyclonal or monoclonal antibodies to the nGPCR-x receptor, and to generate useful antigen-binding fragments thereof or variants thereof, including "humanized" variants. Such protocols can be found, for example, in Sambrook *et al.* (1989) and Harlow *et al.* (Eds.), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988). In one embodiment, recombinant nGPCR-x polypeptides (or cells or cell membranes containing such polypeptides) are used as antigen to generate the antibodies. In another embodiment, one or more peptides having amino acid sequences corresponding to an immunogenic portion of nGPCR-x (*e.g.*, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more amino acids) are used as antigen. Peptides corresponding to extracellular portions of nGPCR-x, especially hydrophilic extracellular portions, are preferred. The antigen may be mixed with an adjuvant or linked to a hapten to increase antibody production.

##### **A. Polyclonal or Monoclonal antibodies**

[000275] As one exemplary protocol, recombinant nGPCR-x or a synthetic fragment thereof is used to immunize a mouse for generation of monoclonal antibodies (or larger mammal, such as a rabbit, for polyclonal antibodies). To increase antigenicity, peptides are conjugated to Keyhole Limpet Hemocyanin (Pierce), according to the manufacturer's recommendations. For an initial injection, the antigen is emulsified with Freund's Complete Adjuvant and injected subcutaneously. At intervals of two to three weeks, additional aliquots of nGPCR-x antigen are emulsified with Freund's Incomplete Adjuvant and injected subcutaneously. Prior to the final booster injection, a serum sample is taken from the immunized mice and assayed by western blot to confirm the presence of antibodies that immunoreact with nGPCR-x. Serum from the immunized animals may be used as polyclonal antisera or used to isolate polyclonal antibodies that recognize nGPCR-x. Alternatively, the mice are sacrificed and their spleen removed for generation of monoclonal antibodies.

[000276] To generate monoclonal antibodies, the spleens are placed in 10 ml serum-free RPMI 1640, and single cell suspensions are formed by grinding the spleens in serum-free RPMI 1640, supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 units/ml penicillin, and 100 µg/ml streptomycin (RPMI) (Gibco, Canada). The cell suspensions are filtered and washed by centrifugation and resuspended in serum-free RPMI. Thymocytes taken from three naive Balb/c mice are prepared in a similar manner and used as a Feeder Layer. NS-1 myeloma cells, kept in log phase in RPMI with 10% fetal bovine serum (FBS) (Hyclone Laboratories, Inc., Logan, Utah) for three days prior to fusion, are centrifuged and washed as well.

[000277] To produce hybridoma fusions, spleen cells from the immunized mice are combined with NS-1 cells and centrifuged, and the supernatant is aspirated. The cell pellet is dislodged by tapping the tube, and 2 ml of 37°C PEG 1500 (50% in 75 mM HEPES, pH 8.0) (Boehringer-Mannheim) is stirred into the pellet, followed by the addition of serum-free RPMI. Thereafter, the cells are centrifuged, resuspended in RPMI containing 15% FBS, 100 µM sodium hypoxanthine, 0.4 µM aminopterin, 16 µM thymidine (HAT) (Gibco), 25 units/ml IL-6 (Boehringer-Mannheim) and  $1.5 \times 10^6$  thymocytes/ml, and plated into 10 Corning flat-bottom 96-well tissue culture plates (Corning, Corning New York).

[000278] On days 2, 4, and 6 after the fusion, 100 µl of medium is removed from the wells of the fusion plates and replaced with fresh medium. On day 8, the fusions are screened by ELISA, testing for the presence of mouse IgG that binds to nGPCR-x. Selected fusion wells are further cloned by dilution until monoclonal cultures producing anti-nGPCR-x antibodies are obtained.

B. Humanization of anti-nGPCR-x monoclonal antibodies

[000279] The expression pattern of nGPCR-x as reported herein and the proven track record of GPCRs as targets for therapeutic intervention suggest therapeutic indications for nGPCR-x

inhibitors (antagonists). nGPCR-x-neutralizing antibodies comprise one class of therapeutics useful as nGPCR-x antagonists. Following are protocols to improve the utility of anti-nGPCR-x monoclonal antibodies as therapeutics in humans by "humanizing" the monoclonal antibodies to improve their serum half-life and render them less immunogenic in human hosts (*i.e.*, to prevent human antibody response to non-human anti-nGPCR-x antibodies).

[000280] The principles of humanization have been described in the literature and are facilitated by the modular arrangement of antibody proteins. To minimize the possibility of binding complement, a humanized antibody of the IgG4 isotype is preferred.

[000281] For example, a level of humanization is achieved by generating chimeric antibodies comprising the variable domains of non-human antibody proteins of interest with the constant domains of human antibody molecules. (See, *e.g.*, Morrison *et al.*, Adv. Immunol., 44:65-92 (1989)). The variable domains of nGPCR-x-neutralizing anti-nGPCR-x antibodies are cloned from the genomic DNA of a B-cell hybridoma or from cDNA generated from mRNA isolated from the hybridoma of interest. The V region gene fragments are linked to exons encoding human antibody constant domains, and the resultant construct is expressed in suitable mammalian host cells (*e.g.*, myeloma or CHO cells).

[000282] To achieve an even greater level of humanization, only those portions of the variable region gene fragments that encode antigen-binding complementarity determining regions ("CDR") of the non-human monoclonal antibody genes are cloned into human antibody sequences. (See, *e.g.*, Jones *et al.*, Nature 321:522-525 (1986); Riechmann *et al.*, Nature 332:323-327 (1988); Verhoeven *et al.*, Science 239:1534-36 (1988); and Tempest *et al.*, Bio/Technology 9: 266-71 (1991)). If necessary, the  $\beta$ -sheet framework of the human antibody surrounding the CDR3 regions also is modified to more closely mirror the three dimensional structure of the antigen-binding domain of the original monoclonal antibody. (See Kettleborough *et al.*, Protein Engin., 4:773-783 (1991); and Foote *et al.*, J. Mol. Biol., 224:487-499 (1992)).

[000283] In an alternative approach, the surface of a non-human monoclonal antibody of interest is humanized by altering selected surface residues of the non-human antibody, *e.g.*, by site-directed mutagenesis, while retaining all of the interior and contacting residues of the non-human antibody. See Padlan, Molecular Immunol., 28(4/5):489-98 (1991).

[000284] The foregoing approaches are employed using nGPCR-x-neutralizing anti-nGPCR-x monoclonal antibodies and the hybridomas that produce them to generate humanized nGPCR-x-neutralizing antibodies useful as therapeutics to treat or palliate conditions wherein nGPCR-x expression or ligand-mediated nGPCR-x signaling is detrimental.

C. Human nGPCR-x-Neutralizing Antibodies from Phage Display

[000285] Human nGPCR-x-neutralizing antibodies are generated by phage display techniques such as those described in Aujame *et al.*, Human Antibodies 8(4):155-168 (1997); Hoogenboom, TIBTECH 15:62-70 (1997); and Rader *et al.*, Curr. Opin. Biotechnol. 8:503-508 (1997), all of which are incorporated by reference. For example, antibody variable regions in the form of Fab fragments or linked single chain Fv fragments are fused to the amino terminus of filamentous phage minor coat protein pIII. Expression of the fusion protein and incorporation thereof into the mature phage coat results in phage particles that present an antibody on their surface and contain the genetic material encoding the antibody. A phage library comprising such constructs is expressed in bacteria, and the library is screened for nGPCR-x-specific phage-antibodies using labeled or immobilized nGPCR-x as antigen-probe.

D. Human nGPCR-x-neutralizing antibodies from transgenic mice

[000286] Human nGPCR-x-neutralizing antibodies are generated in transgenic mice essentially as described in Bruggemann *et al.*, Immunol. Today 17(8):391-97 (1996) and Bruggemann *et al.*, Curr. Opin. Biotechnol. 8:455-58 (1997). Transgenic mice carrying human V-gene segments in germline configuration and that express these transgenes in their lymphoid tissue are immunized with a nGPCR-x composition using conventional immunization protocols. Hybridomas are generated using B cells from the immunized mice using conventional protocols and screened to identify hybridomas secreting anti-nGPCR-x human antibodies (*e.g.*, as described above).

**EXAMPLE 11: ASSAYS TO IDENTIFY MODULATORS OF nGPCR-X ACTIVITY**

[000287] Set forth below are several nonlimiting assays for identifying modulators (agonists and antagonists) of nGPCR-x activity. Among the modulators that can be identified by these assays are natural ligand compounds of the receptor; synthetic analogs and derivatives of natural ligands; antibodies, antibody fragments, and/or antibody-like compounds derived from natural antibodies or from antibody-like combinatorial libraries; and/or synthetic compounds identified by high-throughput screening of libraries; and the like. All modulators that bind nGPCR-x are useful for identifying nGPCR-x in tissue samples (*e.g.*, for diagnostic purposes, pathological purposes, and the like). Agonist and antagonist modulators are useful for up-regulating and down-regulating nGPCR-x activity, respectively, to treat disease states characterized by abnormal levels of nGPCR-x activity. The assays may be performed using single putative modulators, and/or may be performed using a known agonist in combination with candidate antagonists (or *visa versa*).

A. cAMP Assays

[000288] In one type of assay, levels of cyclic adenosine monophosphate (cAMP) are measured in nGPCR-x-transfected cells that have been exposed to candidate modulator compounds.

Protocols for cAMP assays have been described in the literature. (See, *e.g.*, Sutherland *et al.*, *Circulation* 37: 279 (1968); Frandsen *et al.*, *Life Sciences* 18: 529-541 (1976); Dooley *et al.*, *Journal of Pharmacology and Experimental Therapeutics* 283 (2): 735-41 (1997); and George *et al.*, *Journal of Biomolecular Screening* 2 (4): 235-40 (1997)). An exemplary protocol for such an assay, using an Adenylyl Cyclase Activation FlashPlate® Assay from NEN™ Life Science Products, is set forth below.

[000289] Briefly, the nGPCR-x coding sequence (*e.g.*, a cDNA or intronless genomic DNA) is subcloned into a commercial expression vector, such as pzeoSV2 (Invitrogen), and transiently transfected into Chinese Hamster Ovary (CHO) cells using known methods, such as the transfection protocol provided by Boehringer-Mannheim when supplying the FuGENE 6 transfection reagent. Transfected CHO cells are seeded into 96-well microplates from the FlashPlate® assay kit, which are coated with solid scintillant to which antisera to cAMP has been bound. For a control, some wells are seeded with wild type (untransfected) CHO cells. Other wells in the plate receive various amounts of a cAMP standard solution for use in creating a standard curve.

[000290] One or more test compounds (*i.e.*, candidate modulators) are added to the cells in each well, with water and/or compound-free medium/diluent serving as a control or controls. After treatment, cAMP is allowed to accumulate in the cells for exactly 15 minutes at room temperature. The assay is terminated by the addition of lysis buffer containing [<sup>125</sup>I]-labeled cAMP, and the plate is counted using a Packard Topcount™ 96-well microplate scintillation counter. Unlabeled cAMP from the lysed cells (or from standards) and fixed amounts of [<sup>125</sup>I]-cAMP compete for antibody bound to the plate. A standard curve is constructed, and cAMP values for the unknowns are obtained by interpolation. Changes in intracellular cAMP levels of cells in response to exposure to a test compound are indicative of nGPCR-x modulating activity. Modulators that act as agonists of receptors which couple to the G<sub>s</sub> subtype of G proteins will stimulate production of cAMP, leading to a measurable 3-10 fold increase in cAMP levels. Agonists of receptors which couple to the G<sub>i/o</sub> subtype of G proteins will inhibit forskolin-stimulated cAMP production, leading to a measurable decrease in cAMP levels of 50-100%. Modulators that act as inverse agonists will reverse these effects at receptors that are either constitutively active or activated by known agonists.

#### B. Aequorin Assays

[000291] In another assay, cells (*e.g.*, CHO cells) are transiently co-transfected with both a nGPCR-x expression construct and a construct that encodes the photoprotein apoaequorin. In the presence of the cofactor coelenterazine, apoaequorin will emit a measurable luminescence that is proportional to the amount of intracellular (cytoplasmic) free calcium. (See generally, Cobbold,



*et al.* "Aequorin measurements of cytoplasmic free calcium," *In*: McCormack J.G. and Cobbold P.H., eds., *Cellular Calcium: A Practical Approach*. Oxford: IRL Press (1991); Stables *et al.*, *Analytical Biochemistry* 252: 115-26 (1997); and Haugland, *Handbook of Fluorescent Probes and Research Chemicals*. Sixth edition. Eugene OR: Molecular Probes (1996).)

[000292] In one exemplary assay, nGPCR-x is subcloned into the commercial expression vector pzeoSV2 (Invitrogen) and transiently co-transfected along with a construct that encodes the photoprotein apoaequorin (Molecular Probes, Eugene, OR) into CHO cells using the transfection reagent FuGENE 6 (Boehringer-Mannheim) and the transfection protocol provided in the product insert.

[000293] The cells are cultured for 24 hours at 37°C in MEM (Gibco/BRL, Gaithersburg, MD) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin, at which time the medium is changed to serum-free MEM containing 5 µM coelenterazine (Molecular Probes, Eugene, OR). Culturing is then continued for two additional hours at 37°C. Subsequently, cells are detached from the plate using VERSEN (Gibco/BRL), washed, and resuspended at 200,000 cells/ml in serum-free MEM.

[000294] Dilutions of candidate nGPCR-x modulator compounds are prepared in serum-free MEM and dispensed into wells of an opaque 96-well assay plate at 50 µl/well. Plates are then loaded onto an MLX microtiter plate luminometer (Dynex Technologies, Inc., Chantilly, VA). The instrument is programmed to dispense 50 µl cell suspensions into each well, one well at a time, and immediately read luminescence for 15 seconds. Dose-response curves for the candidate modulators are constructed using the area under the curve for each light signal peak. Data are analyzed with SlideWrite, using the equation for a one-site ligand, and EC<sub>50</sub> values are obtained. Changes in luminescence caused by the compounds are considered indicative of modulatory activity. Modulators that act as agonists at receptors which couple to the G<sub>q</sub> subtype of G proteins give an increase in luminescence of up to 100 fold. Modulators that act as inverse agonists will reverse this effect at receptors that are either constitutively active or activated by known agonists.

#### C. Luciferase Reporter Gene Assay

[000295] The photoprotein luciferase provides another useful tool for assaying for modulators of nGPCR-x activity. Cells (*e.g.*, CHO cells or COS 7 cells) are transiently co-transfected with both a nGPCR-x expression construct (*e.g.*, nGPCR-x in pzeoSV2) and a reporter construct which includes a gene for the luciferase protein downstream from a transcription factor binding site, such as the cAMP-response element (CRE), AP-1, or NF-kappa B. Agonist binding to receptors coupled to the G<sub>s</sub> subtype of G proteins leads to increases in cAMP, thereby activating the CRE transcription factor and resulting in expression of the luciferase gene. Agonist binding

to receptors coupled to the G<sub>q</sub> subtype of G protein leads to production of diacylglycerol that activates protein kinase C, which activates the AP-1 or NF-kappa B transcription factors, in turn resulting in expression of the luciferase gene. Expression levels of luciferase reflect the activation status of the signaling events. (See generally, George *et al.*, Journal of Biomolecular Screening 2(4): 235-240 (1997); and Stratowa *et al.*, Current Opinion in Biotechnology 6: 574-581 (1995)). Luciferase activity may be quantitatively measured using, *e.g.*, luciferase assay reagents that are commercially available from Promega (Madison, WI).

[000296] In one exemplary assay, CHO cells are plated in 24-well culture dishes at a density of 100,000 cells/well one day prior to transfection and cultured at 37°C in MEM (Gibco/BRL) supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin. Cells are transiently co-transfected with both a nGPCR-x expression construct and a reporter construct containing the luciferase gene. The reporter plasmids CRE-luciferase, AP-1-luciferase and NF-kappaB-luciferase may be purchased from Stratagene (LaJolla, CA). Transfections are performed using the FuGENE 6 transfection reagent (Boehringer-Mannheim) according to the supplier's instructions. Cells transfected with the reporter construct alone are used as a control. Twenty-four hours after transfection, cells are washed once with PBS pre-warmed to 37°C. Serum-free MEM is then added to the cells either alone (control) or with one or more candidate modulators and the cells are incubated at 37°C for five hours. Thereafter, cells are washed once with ice-cold PBS and lysed by the addition of 100 µl of lysis buffer per well from the luciferase assay kit supplied by Promega. After incubation for 15 minutes at room temperature, 15 µl of the lysate is mixed with 50 µl of substrate solution (Promega) in an opaque-white, 96-well plate, and the luminescence is read immediately on a Wallace model 1450 MicroBeta scintillation and luminescence counter (Wallace Instruments, Gaithersburg, MD).

[000297] Differences in luminescence in the presence versus the absence of a candidate modulator compound are indicative of modulatory activity. Receptors that are either constitutively active or activated by agonists typically give a 3 to 20-fold stimulation of luminescence compared to cells transfected with the reporter gene alone. Modulators that act as inverse agonists will reverse this effect.

D. Intracellular calcium measurement using FLIPR

[000298] Changes in intracellular calcium levels are another recognized indicator of G protein-coupled receptor activity, and such assays can be employed to screen for modulators of nGPCR-x activity. For example, CHO cells stably transfected with a nGPCR-x expression vector are plated at a density of  $4 \times 10^4$  cells/well in Packard black-walled, 96-well plates specially designed to discriminate fluorescence signals emanating from the various wells on the plate.

The cells are incubated for 60 minutes at 37°C in modified Dulbecco's PBS (D-PBS) containing 36 mg/L pyruvate and 1 g/L glucose with the addition of 1% fetal bovine serum and one of four calcium indicator dyes (Fluo-3™ AM, Fluo-4™ AM, Calcium Green™-1 AM, or Oregon Green™ 488 BAPTA-1 AM), each at a concentration of 4 µM. Plates are washed once with modified D-PBS without 1% fetal bovine serum and incubated for 10 minutes at 37°C to remove residual dye from the cellular membrane. In addition, a series of washes with modified D-PBS without 1% fetal bovine serum is performed immediately prior to activation of the calcium response.

[000299] A calcium response is initiated by the addition of one or more candidate receptor agonist compounds, calcium ionophore A23187 (10 µM; positive control), or ATP (4 µM; positive control). Fluorescence is measured by Molecular Device's FLIPR with an argon laser (excitation at 488 nm). (See, *e.g.*, Kuntzweiler *et al.*, Drug Development Research, 44(1):14-20 (1998)). The F-stop for the detector camera was set at 2.5 and the length of exposure was 0.4 milliseconds. Basal fluorescence of cells was measured for 20 seconds prior to addition of candidate agonist, ATP, or A23187, and the basal fluorescence level was subtracted from the response signal. The calcium signal is measured for approximately 200 seconds, taking readings every two seconds. Calcium ionophore A23187 and ATP increase the calcium signal 200% above baseline levels. In general, activated GPCRs increase the calcium signal approximately 10-15% above baseline signal.

E. Mitogenesis Assay

[000300] In a mitogenesis assay, the ability of candidate modulators to induce or inhibit nGPCR-x-mediated cell division is determined. (See, *e.g.*, Lajiness *et al.*, Journal of Pharmacology and Experimental Therapeutics 267(3): 1573-1581 (1993)). For example, CHO cells stably expressing nGPCR-x are seeded into 96-well plates at a density of 5000 cells/well and grown at 37°C in MEM with 10% fetal calf serum for 48 hours, at which time the cells are rinsed twice with serum-free MEM. After rinsing, 80µl of fresh MEM, or MEM containing a known mitogen, is added along with 20µl MEM containing varying concentrations of one or more candidate modulators or test compounds diluted in serum-free medium. As controls, some wells on each plate receive serum-free medium alone, and some receive medium containing 10% fetal bovine serum. Untransfected cells or cells transfected with vector alone also may serve as controls.

[000301] After culture for 16-18 hours, 1µ Ci of [<sup>3</sup>H]-thymidine (2 Ci/mmol) is added to the wells and cells are incubated for an additional 2 hours at 37°C. The cells are trypsinized and collected on filter mats with a cell harvester (Tomtec); the filters are then counted in a Betaplate counter. The incorporation of [<sup>3</sup>H]-thymidine in serum-free test wells is compared to the results achieved

in cells stimulated with serum (positive control). Use of multiple concentrations of test compounds permits creation and analysis of dose-response curves using the non-linear, least squares fit equation:  $A = B \times [C / (D + C)] + G$  where A is the percent of serum stimulation; B is the maximal effect minus baseline; C is the  $EC_{50}$ ; D is the concentration of the compound; and G is the maximal effect. Parameters B, C and G are determined by Simplex optimization.

- [000302] Agonists that bind to the receptor are expected to increase [ $^3H$ ]-thymidine incorporation into cells, showing up to 80% of the response to serum. Antagonists that bind to the receptor will inhibit the stimulation seen with a known agonist by up to 100%.

F. [ $^{35}S$ ]GTP $\gamma$ S Binding Assay

- [000303] Because G protein-coupled receptors signal through intracellular G proteins whose activity involves GTP binding and hydrolysis to yield bound GDP, measurement of binding of the non-hydrolyzable GTP analog [ $^{35}S$ ]GTP $\gamma$ S in the presence and absence of candidate modulators provides another assay for modulator activity. (See, e.g., Kowal *et al*, *Neuropharmacology* 37:179-187 (1998).)

- [000304] In one exemplary assay, cells stably transfected with a nGPCR-x expression vector are grown in 10 cm tissue culture dishes to subconfluence, rinsed once with 5 ml of ice-cold  $Ca^{2+}/Mg^{2+}$ -free phosphate-buffered saline, and scraped into 5 ml of the same buffer. Cells are pelleted by centrifugation (500 x g, 5 minutes), resuspended in TEE buffer (25 mM Tris, pH 7.5, 5 mM EDTA, 5 mM EGTA), and frozen in liquid nitrogen. After thawing, the cells are homogenized using a Dounce homogenizer (one ml TEE per plate of cells), and centrifuged at 1,000 x g for 5 minutes to remove nuclei and unbroken cells.

- [000305] The homogenate supernatant is centrifuged at 20,000 x g for 20 minutes to isolate the membrane fraction, and the membrane pellet is washed once with TEE and resuspended in binding buffer (20 mM HEPES, pH 7.5, 150 mM NaCl, 10 mM  $MgCl_2$ , 1 mM EDTA). The resuspended membranes can be frozen in liquid nitrogen and stored at -70°C until use.

- [000306] Aliquots of cell membranes prepared as described above and stored at -70°C are thawed, homogenized, and diluted into buffer containing 20 mM HEPES, 10 mM  $MgCl_2$ , 1 mM EDTA, 120 mM NaCl, 10  $\mu$ M GDP, and 0.2 mM ascorbate, at a concentration of 10-50  $\mu$ g/ml. In a final volume of 90  $\mu$ l, homogenates are incubated with varying concentrations of candidate modulator compounds or 100  $\mu$ M GTP for 30 minutes at 30°C and then placed on ice. To each sample, 10  $\mu$ l guanosine 5'-O-(3[ $^{35}S$ ]thio) triphosphate (NEN, 1200 Ci/mmol; [ $^{35}S$ ]GTP $\gamma$ S), was added to a final concentration of 100-200 pM. Samples are incubated at 30°C for an additional 30 minutes, 1 ml of 10mM HEPES, pH 7.4, 10 mM  $MgCl_2$ , at 4°C is added and the reaction is stopped by filtration.

[000307] Samples are filtered over Whatman GF/B filters and the filters are washed with 20 ml ice-cold 10 mM HEPES, pH 7.4, 10 mM MgCl<sub>2</sub>. Filters are counted by liquid scintillation spectroscopy. Nonspecific binding of [<sup>35</sup>S]-GTPγS is measured in the presence of 100 μM GTP and subtracted from the total. Compounds are selected that modulate the amount of [<sup>35</sup>S]-GTPγS binding in the cells, compared to untransfected control cells. Activation of receptors by agonists gives up to a five-fold increase in [<sup>35</sup>S]GTPγS binding. This response is blocked by antagonists.

G. MAP Kinase Activity Assay

[000308] Evaluation of MAP kinase activity in cells expressing a GPCR provides another assay to identify modulators of GPCR activity. (See, *e.g.*, Lajiness *et al.*, Journal of Pharmacology and Experimental Therapeutics 267(3):1573-1581 (1993) and Boulton *et al.*, Cell 65:663-675 (1991).)

[000309] In one embodiment, CHO cells stably transfected with nGPCR-x are seeded into 6-well plates at a density of 70,000 cells/well 48 hours prior to the assay. During this 48-hour period, the cells are cultured at 37°C in MEM medium supplemented with 10% fetal bovine serum, 2mM glutamine, 10 U/ml penicillin and 10μg/ml streptomycin. The cells are serum-starved for 1-2 hours prior to the addition of stimulants.

[000310] For the assay, the cells are treated with medium alone or medium containing either a candidate agonist or 200 nM Phorbol ester- myristoyl acetate (*i.e.*, PMA, a positive control), and the cells are incubated at 37°C for varying times. To stop the reaction, the plates are placed on ice, the medium is aspirated, and the cells are rinsed with 1 ml of ice-cold PBS containing 1mM EDTA. Thereafter, 200μl of cell lysis buffer (12.5 mM MOPS, pH 7.3, 12.5 mM glycerophosphate, 7.5mM MgCl<sub>2</sub>, 0.5mM EGTA, 0.5 mM sodium vanadate, 1mM benzamidine, 1mM dithiothreitol, 10 μg/ml leupeptin, 10 μg/ml aprotinin, 2μg/ml pepstatin A, and 1μM okadaic acid) is added to the cells. The cells are scraped from the plates and homogenized by 10 passages through a 23 3/4 G needle, and the cytosol fraction is prepared by centrifugation at 20,000 x g for 15 minutes.

[000311] Aliquots (5-10 μl containing 1-5 μg protein) of cytosol are mixed with 1 mM MAPK Substrate Peptide (APRTPGGRR (SEQ ID NO: 258), Upstate Biotechnology, Inc., N.Y.) and 50μM [γ-<sup>32</sup>P]ATP (NEN, 3000 Ci/mmol), diluted to a final specific activity of ~2000 cpm/pmol, in a total volume of 25μl. The samples are incubated for 5 minutes at 30°C, and reactions are stopped by spotting 20μl on 2 cm<sup>2</sup> squares of Whatman P81 phosphocellulose paper. The filter squares are washed in 4 changes of 1% H<sub>3</sub>PO<sub>4</sub>, and the squares are subjected to liquid scintillation spectroscopy to quantitate bound label. Equivalent cytosolic extracts are incubated without MAPK substrate peptide, and the bound label from these samples are subtracted from

the matched samples with the substrate peptide. The cytosolic extract from each well is used as a separate point. Protein concentrations are determined by a dye binding protein assay (Bio-Rad Laboratories). Agonist activation of the receptor is expected to result in up to a five-fold increase in MAPK enzyme activity. This increase is blocked by antagonists.

#### H. [<sup>3</sup>H]Arachidonic Acid Release

[000312] The activation of GPCRs also has been observed to potentiate arachidonic acid release in cells, providing yet another useful assay for modulators of GPCR activity. (See, e.g., Kanterman *et al.*, Molecular Pharmacology 39:364-369 (1991).) For example, CHO cells that are stably transfected with a nGPCR-x expression vector are plated in 24-well plates at a density of 15,000 cells/well and grown in MEM medium supplemented with 10% fetal bovine serum, 2 mM glutamine, 10 U/ml penicillin and 10 µg/ml streptomycin for 48 hours at 37°C before use. Cells of each well are labeled by incubation with [<sup>3</sup>H]-arachidonic acid (Amersham Corp., 210 Ci/mmol) at 0.5 µCi/ml in 1 ml MEM supplemented with 10mM HEPES, pH 7.5, and 0.5% fatty-acid-free bovine serum albumin for 2 hours at 37°C. The cells are then washed twice with 1 ml of the same buffer.

[000313] Candidate modulator compounds are added in 1 ml of the same buffer, either alone or with 10µM ATP and the cells are incubated at 37°C for 30 minutes. Buffer alone and mock-transfected cells are used as controls. Samples (0.5 ml) from each well are counted by liquid scintillation spectroscopy. Agonists which activate the receptor will lead to potentiation of the ATP-stimulated release of [<sup>3</sup>H]-arachidonic acid. This potentiation is blocked by antagonists.

#### I. Extracellular Acidification Rate

[000314] In yet another assay, the effects of candidate modulators of nGPCR-x activity are assayed by monitoring extracellular changes in pH induced by the test compounds. (See, e.g., Dunlop *et al.*, Journal of Pharmacological and Toxicological Methods 40(1):47-55 (1998).) In one embodiment, CHO cells transfected with a nGPCR-x expression vector are seeded into 12 mm capsule cups (Molecular Devices Corp.) at 4 x 10<sup>5</sup> cells/cup in MEM supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 10 U/ml penicillin, and 10 µg/ml streptomycin. The cells are incubated in this medium at 37°C in 5% CO<sub>2</sub> for 24 hours.

[000315] Extracellular acidification rates are measured using a Cytosensor microphysiometer (Molecular Devices Corp.). The capsule cups are loaded into the sensor chambers of the microphysiometer and the chambers are perfused with running buffer (bicarbonate-free MEM supplemented with 4 mM L-glutamine, 10 units/ml penicillin, 10 µg/ml streptomycin, 26 mM NaCl) at a flow rate of 100 µl/minute. Candidate agonists or other agents are diluted into the running buffer and perfused through a second fluid path. During each 60-second pump cycle, the pump is run for 38 seconds and is off for the remaining 22 seconds. The pH of the running

buffer in the sensor chamber is recorded during the cycle from 43-58 seconds, and the pump is re-started at 60 seconds to start the next cycle. The rate of acidification of the running buffer during the recording time is calculated by the Cytosoft program. Changes in the rate of acidification are calculated by subtracting the baseline value (the average of 4 rate measurements immediately before addition of a modulator candidate) from the highest rate measurement obtained after addition of a modulator candidate. The selected instrument detects 61mV/pH unit. Modulators that act as agonists of the receptor result in an increase in the rate of extracellular acidification compared to the rate in the absence of agonist. This response is blocked by modulators which act as antagonists of the receptor.

#### **Example 12 - Using nGPCR-x proteins to isolate neurotransmitters**

[000316] Isolated nGPCR-x proteins of the present invention can be used to isolate novel or known neurotransmitters (Saito *et al.*, Nature 400: 265-269, 1999). The cDNAs that encode the isolated nGPCR-x can be cloned into mammalian expression vectors and used to stably or transiently transfect mammalian cells including CHO, Cos or HEK293 cells. Receptor expression can be determined by Northern blot analysis of transfected cells and identification of an appropriately sized mRNA band (predicted size from the cDNA). Brain regions shown by mRNA analysis to express each of the nGPCR-x proteins could be processed for peptide extraction using any of several protocols ((Reinscheid R.K. *et al.*, Science 270: 243-247, 1996; Sakurai, T., *et al.*, Cell 92: 573-585, 1998; Hinuma, S., *et al.*, Nature 393: 272-276, 1998). Chromatographic fractions of brain extracts could be tested for ability to activate nGPCR-x proteins by measuring second messenger production such as changes in cAMP production in the presence or absence of forskolin, changes in inositol 3-phosphate levels, changes in intracellular calcium levels or by indirect measures of receptor activation including receptor stimulated mitogenesis, receptor mediated changes in extracellular acidification or receptor mediated changes in reporter gene activation in response to cAMP or calcium (these methods should all be referenced in other sections of the patent). Receptor activation could also be monitored by co-transfecting cells with a chimeric  $GI_{q/13}$  to force receptor coupling to a calcium stimulating pathway (Conklin *et al.*, Nature 363: 274-276, 1993). Neurotransmitter mediated activation of receptors could also be monitored by measuring changes in [ $^{35}$ S]-GTPKS binding in membrane fractions prepared from transfected mammalian cells. This assay could also be performed using baculoviruses containing nGPCR-x proteins infected into SF9 insect cells.

[000317] The neurotransmitter which activates nGPCR-x proteins can be purified to homogeneity through successive rounds of purification using nGPCR-x proteins activation as a measurement of neurotransmitter activity. The composition of the neurotransmitter can be determined by

mass spectrometry and Edman degradation if peptidergic. Neurotransmitters isolated in this manner will be bioactive materials which will alter neurotransmission in the central nervous system and will produce behavioral and biochemical changes.

**Example 13 - Using nGPCR-x proteins to isolate and purify G proteins**

[000318] cDNAs encoding nGPCR-x proteins are epitope-tagged at the amino terminus end of the cDNA with the cleavable influenza-hemagglutinin signal sequence followed by the FLAG epitope (IBI, New Haven, CT). Additionally, these sequences are tagged at the carboxyl terminus with DNA encoding six histidine residues. (Amino and Carboxyl Terminal Modifications to Facilitate the Production and Purification of a G Protein-Coupled Receptor, B.K. Kobilka, *Analytical Biochemistry*, Vol. 231, No. 1, Oct 1995, pp. 269-271). The resulting sequences are cloned into a baculovirus expression vector such as pVL1392 (Invitrogen). The baculovirus expression vectors are used to infect SF-9 insect cells as described (Guan, X. M., Kobilka, T. S., and Kobilka, B. K. (1992) *J. Biol. Chem.* 267, 21995-21998). Infected SF-9 cells could be grown in 1000-ml cultures in SF900 II medium (Life Technologies, Inc.) containing 5% fetal calf serum (Gemini, Calabasas, CA) and 0.1 mg/ml gentamicin (Life Technologies, Inc.) for 48 hours at which time the cells could be harvested. Cell membrane preparations could be separated from soluble proteins following cell lysis. nGPCR-x protein purification is carried out as described for purification of the 92 receptor (Kobilka, *Anal. Biochem.*, 231 (1): 269-271, 1995) including solubilization of the membranes in 0.8-1.0 %n-dodecyl -D-maltoside (DM) (CalBiochem, La Jolla, CA) in buffer containing protease inhibitors followed by Ni-column chromatography using chelating Sepharose™ (Pharmacia, Uppsala, Sweden). The eluate from the Ni-column is further purified on an M1 anti-FLAG antibody column (IBI). Receptor containing fractions are monitored by using receptor specific antibodies following western blot analysis or by SDS-PAGE analysis to look for an appropriate sized protein band (appropriate size would be the predicted molecular weight of the protein).

[000319] This method of purifying G protein is particularly useful to isolate G proteins that bind to the nGPCR-x proteins in the absence of an activating ligand.

[000320] Some of the preferred embodiments of the invention described above are outlined below and include, but are not limited to, the following embodiments. As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.



[000321] The entire disclosure of each publication cited herein is hereby incorporated by reference.

**What is claimed is:**

1. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence homologous to sequences selected from the group consisting of: SEQ ID NO:129 to SEQ ID NO:257; said nucleic acid molecule encoding at least a portion of nGPCR-x.
2. The isolated nucleic acid molecule of claim 1 comprising a sequence that encodes a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257.
3. The isolated nucleic acid molecule of claim 1 comprising a sequence homologous to a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128.
4. The isolated nucleic acid molecule of claim 1 comprising a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128.
5. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is DNA.
6. The isolated nucleic acid molecule of claim 1 wherein said nucleic acid molecule is RNA.
7. An expression vector comprising a nucleic acid molecule of any one of claims 1 to 4.
8. The expression vector of claim 7 wherein said nucleic acid molecule comprises a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128.
9. The expression vector of claim 7 wherein said vector is a plasmid.
10. The expression vector of claim 7 wherein said vector is a viral particle.
11. The expression vector of claim 10 wherein said vector is selected from the group consisting of adenoviruses, baculoviruses, parvoviruses, herpesviruses, poxviruses, adeno-associated viruses, Semliki Forest viruses, vaccinia viruses, and retroviruses.

12. The expression vector of claim 7 wherein said nucleic acid molecule is operably connected to a promoter selected from the group consisting of simian virus 40, mouse mammary tumor virus, long terminal repeat of human immunodeficiency virus, maloney virus, cytomegalovirus immediate early promoter, Epstein Barr virus, rous sarcoma virus, human actin, human myosin, human hemoglobin, human muscle creatine, and human metallothionein.
13. A host cell transformed with an expression vector of claim 7.
14. The transformed host cell of claim 13 wherein said cell is a bacterial cell.
15. The transformed host cell of claim 14 wherein said bacterial cell is *E. coli*.
16. The transformed host cell of claim 13 wherein said cell is yeast.
17. The transformed host cell of claim 16 wherein said yeast is *S. cerevisiae*.
18. The transformed host cell of claim 13 wherein said cell is an insect cell.
19. The transformed host cell of claim 18 wherein said insect cell is *S. frugiperda*.
20. The transformed host cell of claim 13 wherein said cell is a mammalian cell.
21. The transformed host cell of claim 20 wherein mammalian cell is selected from the group consisting of chinese hamster ovary cells, HeLa cells, African green monkey kidney cells, human HEK-293 cells, and murine 3T3 fibroblasts.
22. An isolated nucleic acid molecule comprising at least 10 nucleotides, said nucleic acid molecule comprising a nucleotide sequence complementary to at least a portion of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128.
23. The nucleic acid molecule of claim 22 wherein said molecule is an antisense oligonucleotide directed to a region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128.

24. The nucleic acid molecule of claim 23 wherein said oligonucleotide is directed to a regulatory region of a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128.
25. A composition comprising a nucleic acid molecule of any one of claims 1 to 4 or 22 and an acceptable carrier or diluent.
26. A composition comprising a recombinant expression vector of claim 7 and an acceptable carrier or diluent.
27. A method of producing a polypeptide that comprises a sequence selected from the group of sequences consisting SEQ ID NO:129 to SEQ ID NO:257, and homologs thereof, said method comprising the steps of:
- a) introducing a recombinant expression vector of claim 8 into a compatible host cell;
  - b) growing said host cell under conditions for expression of said polypeptide; and
  - c) recovering said polypeptide.
28. The method of claim 27 wherein said host cell is lysed and said polypeptide is recovered from the lysate of said host cell.
29. The method of claim 27 wherein said polypeptide is recovered by purifying the culture medium without lysing said host cell.
30. An isolated polypeptide encoded by a nucleic acid molecule of claim 1.
31. The polypeptide of claim 30 wherein said polypeptide comprises a sequence selected from the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257.
32. The polypeptide of claim 30 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257.

33. The polypeptide of claim 30 wherein said sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257 comprises at least one conservative amino acid substitution compared to the sequences in the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257.
34. The polypeptide of claim 30 wherein said polypeptide comprises an allelic variant of a polypeptide with a sequence selected from the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257.
35. A composition comprising a polypeptide of claim 34 and an acceptable carrier or diluent.
36. An isolated antibody which binds to an epitope on a polypeptide of claim 30.
37. The antibody of claim 36 wherein said antibody is a monoclonal antibody.
38. A composition comprising an antibody of claim 36 and an acceptable carrier or diluent.
39. A method of inducing an immune response in a mammal against a polypeptide of claim 30 comprising administering to said mammal an amount of said polypeptide sufficient to induce said immune response.
40. A method for identifying a compound which binds nGPCR-x comprising the steps of:
- a) contacting nGPCR-x with a compound; and
  - b) determining whether said compound binds nGPCR-x.
41. The method of claim 40 wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257.
42. The method of claim 40 wherein binding of said compound to nGPCR-x is determined by a protein binding assay.
43. The method of claim 40 wherein said protein binding assay is selected from the group consisting of a gel-shift assay, Western blot, radiolabeled competition assay, phage-based expression cloning, co-fractionation by chromatography, co-precipitation, cross linking, interaction trap/two-hybrid analysis, southwestern analysis, and ELISA.

44. A compound identified by the method of claim 40.
45. A method for identifying a compound which binds a nucleic acid molecule encoding nGPCR-x comprising the steps of:
- a) contacting said nucleic acid molecule encoding nGPCR-x with a compound; and
  - b) determining whether said compound binds said nucleic acid molecule.
46. The method of claim 45 wherein binding is determined by a gel-shift assay.
47. A compound identified by the method of claim 45.
48. A method for identifying a compound which modulates the activity of nGPCR-x comprising the steps of:
- a) contacting nGPCR-x with a compound; and
  - b) determining whether nGPCR-x activity has been modulated.
49. The method of claim 48 wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:129 to SEQ IDNO:257.
50. The method of claim 48 wherein said activity is neuropeptide binding.
51. The method of claim 48 wherein said activity is neuropeptide signaling.
52. A compound identified by the method of claim 48.
53. A method of identifying an animal homolog of nGPCR-x comprising the steps:
- a) comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequence consisting of SEQ ID NO:1 to SEQ ID NO:128, and portions thereof, said portions being at least 10 nucleotides; and
  - b) identifying nucleic acid sequences of the animal that are homologous to said sequence selected from the group sequence consisting of SEQ ID NO:1 to SEQ ID NO:128, and portions thereof, said portions comprising at least 10 nucleotides.

54. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128, and portions thereof, said portions being at least 10 nucleotides, is performed by DNA hybridization.

55. The method of claim 53 wherein comparing the nucleic acid sequences of the animal with a sequence selected from the group of sequences consisting of SEQ ID NO:1 to SEQ ID NO:128, and portions thereof, said portions being at least 10 nucleotides, is performed by computer homology search.

56. A method of screening a human subject to diagnose a disorder affecting the brain or genetic predisposition therefor, comprising the steps of:

(a) assaying nucleic acid of a human subject to determine a presence or an absence of a mutation altering an amino acid sequence, expression, or biological activity of at least one nGPCR-x that is expressed in the brain, wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, and allelic variants thereof, and wherein the nucleic acid corresponds to a gene encoding the nGPCR-x; and

(b) diagnosing the disorder or predisposition from the presence or absence of said mutation, wherein the presence of a mutation altering the amino acid sequence, expression, or biological activity of the nGPCR-x in the nucleic acid correlates with an increased risk of developing the disorder.

57. A method according to claim 56, wherein the disease is a mental disorder.

58. A method according to claim 56, wherein the assaying step comprises at least one procedure selected from the group consisting of:

a) comparing nucleotide sequences from the human subject and reference sequences and determining a difference of at least a nucleotide of at least one codon between the nucleotide sequences from the human subject that encodes a nGPCR-x reference sequence;

(b) performing a hybridization assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences;

(c) performing a polynucleotide migration assay to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences; and

(d) performing a restriction endonuclease digestion to determine whether nucleic acid from the human subject has a nucleotide sequence identical to or different from one or more reference sequences.

59. A method according to claim 58 wherein the assaying step comprises: performing a polymerase chain reaction assay to amplify nucleic acid comprising nGPCR-x coding sequence, and determining nucleotide sequence of the amplified nucleic acid.

60. A method of screening for an nGPCR-x hereditary mental disorder genotype in a human patient, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from said patient, said nucleic acid including sequences corresponding to alleles of nGPCR-x; and

(b) detecting the presence of one or more mutations in the nGPCR-x allele;

wherein the presence of a mutation in a nGPCR-x allele is indicative of a hereditary mental disorder genotype.

61. The method according to claim 60 wherein said biological sample is a cell sample.

62. The method according to claim 60 wherein said detecting the presence of a mutation comprises sequencing at least a portion of said nucleic acid, said portion comprising at least one codon of said nGPCR-x allele, said portion comprising at least 10 nucleotides.

63. The method according to claim 60 wherein said nucleic acid is DNA.

64. The method according to claim 60 wherein said nucleic acid is RNA.

65. A kit for screening a human subject to diagnose a mental disorder or a genetic predisposition therefor, comprising, in association:

(a) an oligonucleotide useful as a probe for identifying polymorphisms in a human nGPCR-x gene, the oligonucleotide comprising 6-50 nucleotides in a sequence that is identical or complementary to a sequence of a wild type human nGPCR-x gene sequence or



nGPCR-x coding sequence, except for one sequence difference selected from the group consisting of a nucleotide addition, a nucleotide deletion, or nucleotide substitution; and

(b) a media packaged with the oligonucleotide, said media containing information for identifying polymorphisms that correlate with mental disorder or a genetic predisposition therefor, the polymorphisms being identifiable using the oligonucleotide as a probe.

66. A method of identifying a nGPCR-x allelic variant that correlates with a mental disorder, comprising the steps of:

(a) providing a biological sample comprising nucleic acid from a human patient diagnosed with a mental disorder, or from the patient's genetic progenitors or progeny;

(b) detecting in the nucleic acid the presence of one or more mutations in an nGPCR-x that is expressed in the brain, wherein the nGPCR-x comprises an amino acid sequence selected from the group consisting of SEQ ID NO:129 to SEQ ID NO:257, and allelic variants thereof, and wherein the nucleic acid includes sequence corresponding to the gene or genes encoding nGPCR-x;

wherein the one or more mutations detected indicates an allelic variant that correlates with a mental disorder.

67. A purified and isolated polynucleotide comprising a nucleotide sequence encoding a nGPCR-x allelic variant identified according to claim 66.

68. A host cell transformed or transfected with a polynucleotide according to claim 67 or with a vector comprising the polynucleotide.

69. A purified polynucleotide comprising a nucleotide sequence encoding nGPCR-x of a human with a mental disorder;

wherein said polynucleotide hybridizes to the complement of a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 under the following hybridization conditions:

(a) hybridization for 16 hours at 42°C in a hybridization solution comprising 50% formamide, 1% SDS, 1 M NaCl, 10% dextran sulfate and

(b) washing 2 times for 30 minutes at 60°C in a wash solution comprising 0.1x SSC and 1% SDS; and

wherein the polynucleotide that encodes nGPCR-x amino acid sequence of the human differs from the sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 by at least one residue.

70. A vector comprising a polynucleotide according to claim 69.

71. A host cell that has been transformed or transfected with a polynucleotide according to claim 69 and that expresses the nGPCR-x protein encoded by the polynucleotide.

72. A host cell according to claim 71 that has been co-transfected with a polynucleotide encoding the nGPCR-x amino acid sequence set forth in a sequence selected from the group consisting of SEQ ID NO:1 to SEQ ID NO:128 and that expresses the nGPCR-x protein having the amino acid sequence set forth in SEQ ID NO:129 to SEQ ID NO:257.

73. A method for identifying a modulator of biological activity of nGPCR-x comprising the steps of:

a) contacting a cell according to claim 72 in the presence and in the absence of a putative modulator compound;

b) measuring nGPCR-x biological activity in the cell;

wherein decreased or increased nGPCR-x biological activity in the presence versus absence of the putative modulator is indicative of a modulator of biological activity.

74. A method to identify compounds useful for the treatment of a mental disorder, said method comprising the steps of:

(a) contacting a composition comprising nGPCR-x with a compound suspected of binding nGPCR-x;

(b) detecting binding between nGPCR-x and the compound suspected of binding nGPCR-x;

wherein compounds identified as binding nGPCR-x are candidate compounds useful for the treatment of a mental disorder.

75. A method for identifying a compound useful as a modulator of binding between nGPCR-x and a binding partner of nGPCR-x comprising the steps of:

(a) contacting the binding partner and a composition comprising nGPCR-x in the presence and in the absence of a putative modulator compound;

(b) detecting binding between the binding partner and nGPCR-x; wherein decreased or increased binding between the binding partner and nGPCR-x in the presence of the putative modulator, as compared to binding in the absence of the putative modulator is indicative a modulator compound useful for the treatment of a mental disorder.

76. A method according to claim 74 or 75 wherein the composition comprises a cell expressing nGPCR-x on its surface.

77. A method according to claim 76 wherein the composition comprises a cell transformed or transfected with a polynucleotide that encodes nGPCR-x.

78. A method of purifying a G protein from a sample containing said G protein comprising the steps of:

- a) contacting said sample with a polypeptide of claim 1 for a time sufficient to allow said G protein to form a complex with said polypeptide;
- b) isolating said complex from remaining components of said sample;
- c) maintaining said complex under conditions which result in dissociation of said G protein from said polypeptide; and
- d) isolating said G protein from said polypeptide.

79. The method of claim 78 wherein said sample comprises an amino acid sequence selected from the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257.

80. The method of claim 78 wherein said polypeptide comprises an amino acid sequence homologous to a sequence selected from the group of sequences consisting of SEQ ID NO:129 to SEQ ID NO:257.

81. The method of claim 78 wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: SEQ ID NO:129 to SEQ ID NO:257.

## SEQUENCE LISTING

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<212> DNA  
<213> Homo sapiens

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 <212> DNA  
 <213> Homo sapiens

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<210> 11  
 <211> 502  
 <212> DNA  
 <213> Homo sapiens

<400> 11  
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 <212> DNA  
 <213> Homo sapiens

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<210> 13  
 <211> 1000  
 <212> DNA  
 <213> Homo sapiens

<400> 13  
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<210> 14  
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<212> DNA  
<213> Homo sapiens

<400> 14  
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<210> 15  
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<213> Homo sapiens

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<210> 16
<211> 630
<212> DNA
<213> Homo sapiens

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<400> 16
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gattagtggg tgctggtagt taaggagggg tagaagcatc cggacggtgg ttatgaaaag 480
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ggttaaaggg tatactcttc atattatttc 630

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<210> 17
<211> 314
<212> DNA
<213> Homo sapiens

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<400> 17
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atTTTTtttc agtgcatttg tatcttctaa ttttctcata gtaatatcac aggggtcccca 180

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<210> 18  
<211> 181  
<212> DNA  
<213> Homo sapiens

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t 181

<210> 19  
<211> 594  
<212> DNA  
<213> Homo sapiens

<400> 19  
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<210> 20  
<211> 391  
<212> DNA  
<213> Homo sapiens

<400> 20  
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ccggcgagtc cgagctgcac tgcggggccg ctaccttcag acttcctgt acgctccaca 300

cttccacaac gggcgaggct actttttataa tcataaaaaa tgcccaatca atacaatttt 360  
caaaagaaga agcggaaggg aaaaaccaat c 391

<210> 21  
<211> 363  
<212> DNA  
<213> Homo sapiens

<400> 21  
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<210> 22  
<211> 731  
<212> DNA  
<213> Homo sapiens

<400> 22  
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<210> 23  
<211> 624  
<212> DNA  
<213> Homo sapiens

<400> 23

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<210> 24
<211> 555
<212> DNA
<213> Homo sapiens

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<400> 24
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<210> 25
<211> 776
<212> DNA
<213> Homo sapiens

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<210> 26  
 <211> 651  
 <212> DNA  
 <213> Homo sapiens

<400> 26  
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<210> 27  
 <211> 362  
 <212> DNA  
 <213> Homo sapiens

<400> 27  
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362

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 <212> DNA  
 <213> Homo sapiens

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 <211> 609  
 <212> DNA  
 <213> Homo sapiens

<400> 29  
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 tgtaacatac aaaacccaaa gagagtaaaa cagagcatac tgaaatcttg acacctctca 420  
 aagaactaga tggtttaccc ttttacatag gaagcaaata aaggagaaac tgtcaatgac 480  
 tgatgggaac acagtacaaa atttaagtta gtggtttatt tttaaagctt gtataaatg 540  
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 agcttttttc 609

<210> 30  
 <211> 689  
 <212> DNA  
 <213> Homo sapiens

<400> 30



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cgaaccatag caaatgtctt gaaggtaaga attctctacc acaagcttct ctgctgggta 360
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gatctcaatt tacaaaatgg gggtaaccag gtggcctaga taaatcttga tagatataca 540
gagagaggta aagtagtgaa agccctatga aaaatgtaat tcaatatgaa aacgtatggt 600
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gaagggaagc attacaagct aagctggct 689

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<210> 31
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<212> DNA
<213> Homo sapiens

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cctgtgtttt atttatgtct aaaacatagg taaacggtgt atgtatgatg tcttcttctt 240
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caaccaacca accttgaaaa acttaaaaa tgaacaaaga gaaaagaaat tacctaacat 360
caaacataat gtgtatacat tacaaaagct tgaaaaatac agaaaaacac aaaggaaaga 420
aaaaaaaaatc acttccactc aaaattattt ctgttaattt cagtatatag ccaagcattt 480
ttccatgtat 490

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<210> 32
<211> 634
<212> DNA
<213> Homo sapiens

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<400> 32
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ggaaagaaat taaagctgct acaactagac agtcagaagt tgctcagaag tggtagtctt 180
aaatgttctt aaggagagcta ctctggtttg gttatggttt gtctgtcccc accaaacctc 240
atgttgacat tttcttccca gtgtggcagt gttgagaggt gaggcctagt gggaggtgtc 300

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tgggtcatgg aggtggatcc ctcatgaaca cttagtgtctg ctctcaagtt agtgagttct 360  
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 gacataaagc cacatgcctt tcacatgtgt ccacttcccc ttgaccttc tctaccatgt 480  
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<210> 33  
 <211> 602  
 <212> DNA  
 <213> Homo sapiens

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 gaagaatttt aaccaagcca atggattttt attattttata cttatttaaag attattttga 180  
 ctgcagtgtg gagaatagag tagaaagaaa tagagaagta aggaacctac tgctatttca 240  
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 gccaaatata agatataaac gggagtatac atgccaggac ttgttgatgg attacatact 360  
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 tatacattat tctagatgtg ttgactaca aatgacagaa atttaattaa aatgcaattt 480  
 gataaagaat ttactcataa gtcataattgt ctcatatgac tgggaaatct aagggtgagt 540  
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 <212> DNA  
 <213> Homo sapiens

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 cttactgttc taagactttt ggaactatct gttttatccc ctactttttc caactacatt 180  
 gtgtattact cctactggtg taaatattta ccaaagaaaa ttttttact ttaatatc 238

<210> 35  
 <211> 478  
 <212> DNA  
 <213> Homo sapiens

<400> 35  
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agttatgctt gtagaagcca actcaagatt aatttacata tttaaaaata ttttccttgg 120  
 aaatttaata cacatccaat atcgattatc ttctttaagt actttgtatc ttattcttcc 180  
 tgtcaagctt tgcactataa aggtgatgtc atgcttttct gccatgcctc atgcagggtg 240  
 cacctccttc ctcaccccca cgtcttttcc aggtgagccg cgatgcgcaa aaggttggga 300  
 tgcttggcac aggatgccag ctagtcatg tctttagaat gcccctgtg tctctccgg 360  
 ggctaaatcc tattccaccg tgagccttcc ttgaccagca gagaatagaa gcgcctgggtg 420  
 catacaggcc accaaaggta tctgttgaac agacatgcac acggcttctg ccgtgggc 478

<210> 36  
 <211> 615  
 <212> DNA  
 <213> Homo sapiens

<400> 36  
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 gtgttgaac taagaaaata cagagggcat taagagaacc tatgaggtaa ctttgacttc 180  
 acttcagggg cctggaagga ggaagcaaca atcctaagtg aaacttggac aagaagcacc 240  
 caataggtag acaaagggat tgagggtatg agttgttagt gaacagaggg aaagaagaga 300  
 gtgactcaca aaagaagaac acaatttttg aggctaatta caagttagaa ataaaataat 360  
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 agtagtaact tgggtgattt ttataatttc tcagaacttc acaaaggtag gagaaaatca 540  
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<210> 37  
 <211> 392  
 <212> DNA  
 <213> Homo sapiens

<400> 37  
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 ttgcaaaagt ttatttgcag aagttgtttt tgcaaaagt gaagagtaga taatccaac 180  
 tttccatatt catagtgtc acaagtcgat taacaaacca actcttaact ccttttccag 240  
 aaaaatgctt tgcattaaca aaagtggaga tacttagatt gatttgctcc attagctgga 300  
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<210> 38  
<211> 715  
<212> DNA  
<213> Homo sapiens

<400> 38  
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accaaaaaaaa aaaaaaaaaa cccaaaagta aaacgtttga taacagaatg tgggtgctggg 180  
acatgaggca gacagtagta atttacagtg tcatttatcg gttgccattt acatgtcgg 240  
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gccaggcaaa ctctttgttg atttcattgg ggtggatcct aaaatccaat caggccacaa 420  
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<210> 39  
<211> 596  
<212> DNA  
<213> Homo sapiens

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tgtgcctttt tattacttga ggtatatgga gtctctaatt taaggctaaa tataaaataa 180  
agcatacaca gctggacttt caagtatttt caaaacacat ttaatacctt cccgtgaaac 240  
gccagaatc tgagcaggca tcaacttcgca ccagtataaa caggagtgg cgtggaccga 300  
acgtacgggc ttcaaaagca tatttaagag ggttgaaacag gaacctgcaa gccagaggcc 360  
tgaagggatc gcaatgctga cctgagctca cagtcacaca gtgtcctttg ccacaccagg 420  
gctataatag aaaccagcaa agctgggtga cacggccaac accaacaggg tctgcctctg 480  
accgcagctt tgccctgccc ccacgtactt ttcggctctg ttcctccact ccagggccaa 540  
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<210> 40  
<211> 494  
<212> DNA  
<213> Homo sapiens

<400> 40

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 gagcaaatca atctaagtat ctccactttt gttaatgcaa agcatttttc tggaaaagga 180  
 gttaagagtt ggtttgttaa tcgacttggtg agcactatga atatggaaag ttgggattat 240  
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 aggataatct ttgaagtgtt gctatcctct gctcaggaga ggaattaagc atattgggta 360  
 gattctctga ggccagtcag tggattttac ccctgacagc tatcagaaga aagatgtgaa 420  
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 tttccacttt gaag 494

<210> 41  
 <211> 542  
 <212> DNA  
 <213> Homo sapiens

<400> 41  
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 ctctgcatgt cagactgtag actgggctct ccagtcaccc tagccagtgt tttctggggt 180  
 gcagtggttc ccagcctccc tgggatggag gtccctgtgg gagggatggg ccaccatctt 240  
 tgctgttaca cagccttagc cattgttgcc tttgagctct agggattctg aggtgactag 300  
 ggactggaaa agtccccag aacagtgcag ctgctctatg gataaacagc cagactgcat 360  
 tttcacatgg gtccgaggtc ctagtctct tccccaggca gaatttctg accacagtct 420  
 atgaccaccc ccaccagtgt tttctgggtc gcagcagttt ccaacctccc tgggatgggg 480  
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<210> 42  
 <211> 708  
 <212> DNA  
 <213> Homo sapiens

<400> 42  
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 tgtggcctgt ggcagacaac cctgtccatc cccccacttc ctggctagca gaactctgat 240  
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 aaggtggcca aaaaactaag tcctggccaa tgttttgtaa gcagacatct atgggcgggt 360  
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tctctcttct ggtttgaaa gcgactaca cttgctgct tccaaaaggc agaaggagct 480  
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 aagccattgt ggttggctgt gttacatgca gccaaatatg attattgata cgtgagggtc 600  
 ttctctgaac tcatactgat atgagccaag caatttaaac atgtttaatg gggcctttaa 660  
 aatggcatcc gggctgggca cgggtggctca cgcctgtaat ctacagcac 708

<210> 43  
 <211> 592  
 <212> DNA  
 <213> Homo sapiens

<400> 43  
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 gatggagagc gtgcagtgcc gcctcatggg gttcctggcc atgctgtcca ccgaagtctc 120  
 tgttctgcta ctgacctact tgactttgga gaagttcctg gtcattgtct tccccttcag 180  
 taacattcga cctggaaaac ggcagacctc agtcacctc atttgcactc ggatggcggg 240  
 atttttaata gctgtaattc cattttggaa taaggattat tttggaaact tttatgggaa 300  
 aaatggagta tgtttccac tttattatga ccaaacagaa gatattggaa gcaaagggta 360  
 ttctcttgga attttcctag gtaaattata ttttttcatt tcctggaaaa acataatttt 420  
 gctagaaata cgttaaattt cagcaaagggt ggatttgttt gtttcagaaa gtgagataac 480  
 atagtcaaga ctgtgtcctt tttcacacaa aaaagttttt actattgtgt ttattgaagt 540  
 tttattaaac tttttattag acaatattta gtgtggaaaa taaagacata ct 592

<210> 44  
 <211> 459  
 <212> DNA  
 <213> Homo sapiens

<400> 44  
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 atgttttcag tttcctttta ttgatagaaa atttacatgc agtaaaatgc acagaacttc 180  
 agtatacaat tcaattattt tggataaata tgtacacctt ggcaattgac atctcaatca 240  
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 ctccatcac caaccatgtt tctggtttct attgccatat attagtttat cttgtccttg 360  
 aatttcacgt aaatggaatc atacactgtg ttctcttctg tgccttcttg aactcaatgt 420  
 aacattttga gatgcatttt atattacagg atgtaccta 459

<210> 45  
 <211> 616  
 <212> DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 45

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aaaataaaaa ggtagcaaaa cctcctccta atcctactaa gataatcagg attcccagaa      180
tgggattgat tataagcctc catacaaaact cagcattgtc ttttattttt aaatcagtta      240
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agatgttaatt ttattttctg tgatctttca aaaattttct atgctggata aactacaaat      480
aaacacaaac tttcttgaaa ggaaaatata taggatttgt aaatattaat tttgaaaatg      540
ttttcttttt aatattgctg attcttacac ttcattccaa gtacttatta tatttttttag      600
gagatatata agttag                                     616

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&lt;210&gt; 46

&lt;211&gt; 525

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 46

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taattttacc tacttagggg ctctctctat ttttcctttc agttcatgtt aatttctaaa      120
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gttttcatag gaaatttagg actgtatgat cctaaattgt gctggagtac cacattttct      240
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gaataaaaact tctctagagc ttcacaatct aataagatag gcatttataa atatctctta      480
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&lt;210&gt; 47

&lt;211&gt; 526

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 47

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ttacacagga agtacagctc ctgaggcaat agaattctta tgtagaatg tatacttatt      180
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 aaatttagta attagcaata ggtctcagtt catttaatgt gaatgagcaa gatctcagct 480  
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<210> 48  
 <211> 575  
 <212> DNA  
 <213> Homo sapiens

<400> 48  
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 cacctctccc ccataccagc agattcttga cagcctgcaa ctctctatca agggaaaacc 480  
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<210> 49  
 <211> 678  
 <212> DNA  
 <213> Homo sapiens

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678

<210> 50  
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<212> DNA  
<213> Homo sapiens

<400> 50  
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aaaacattaa tttcttttga gtatgactgc cccacatttc tttttggtt tctccttggg 540  
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<210> 51  
<211> 355  
<212> DNA  
<213> Homo sapiens

<400> 51  
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cttagttgtt tgttgtaatg gataaaaaaa tgacagcaca ggtggttaagc attcatatag 180  
atcaaaggca gagttttctg tcttgctatg caacacaatc acctgaatat ctgatatagt 240  
aaacactcct gggtaattcc aatatgctgc caaggttgag aacgactcaa actttcagca 300  
cctctgggta ttactattac atactatagc acacagttag gtgtgttata tcaaa 355

<210> 52  
<211> 637  
<212> DNA  
<213> Homo sapiens

<400> 52  
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tgcacgggat ggtctacaca tctctgattg caataacaca accagtctga taatattctg 180  
tacatggact catagcatat tttatggctt acaaaataat agtcaaatgc taataaataa 240  
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ctaaaaataat ttataaaatt tgtctactca tgttcagcag tggagttctg agattaattt 360  
 ttttttcctt tcataagtca agacaatggg gaattttaat tctgtaaaga ctcaacatcc 420  
 ttctctccca cttcatttgg taattgtctt ctttcatgac tgaattcctc ttagtcttag 480  
 cctgagtcce actttgtgct tattccacaa tgatgtctgc tgtgaggcca tttccttacc 540  
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 ttgaactaca gagtctttgg cagctgcac aaaagga 637

<210> 53  
 <211> 680  
 <212> DNA  
 <213> Homo sapiens

<400> 53  
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 gttacacttg gatagaaatt ttttcgcac attttgtact agcttgcac agttatttgg 300  
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 cattctgcca gttattttcc ttgaagtgc aggctaactt tgttattttc ttaagagaat 540  
 gtgtgcaaaa tatccaagtc tgagtaacca tagttcgtct gtcagtgggt ttttaagtgg 600  
 aaatgatgtt ccattaaaaa aagtggctaa ttcattctcat aactcaatcg tgtaagtact 660  
 tttctggaa gtgaccattc 680

<210> 54  
 <211> 583  
 <212> DNA  
 <213> Homo sapiens

<400> 54  
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 atagtatctg gcatgaaata gatgcttaat gaactatttg tttaatggat gttgatcatt 240  
 tgtgttgggt actttacaag gttacattt ttttccatgt tgaggacatg ggcaaactgt 300  
 cctatggctt gtggctgtga tgatgcattg cagcactggg gtgcttccga ctggtctgct 360  
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<210> 55  
<211> 634  
<212> DNA  
<213> Homo sapiens

<400> 55  
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tttacggtcc ttgatacatc ttttcaccaa tttcaactga aatatatatg taaacatagg 180  
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aataaaaaaa atcaaattct gtgagcaaca cataatatat gttcaggatt agaataaaac 300  
tatctgcatg aaaaatgttt agaagaacct ctattcatcc aaaaatatct tctccttgtc 360  
cacaaaccag ggtttgtgca agcctggaaa ttaaattggca taccctttcc tgagtgtctac 420  
tattcctgag tgctactagg ccagggtttt ggcctaggta ctgttgctcg cagcacagaa 480  
agccaatcac tgagacaaag agtagtgcca aggaagaagg ctttaatttg gtgctgaagt 540  
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tatacagcag ggggaaaata taagtatgtg tgag 634

<210> 56  
<211> 431  
<212> DNA  
<213> Homo sapiens

<400> 56  
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tgctgataac accagaagac ccctacattc tctactcaat aggagagcta atgaggtggc 180  
atgtgatgta gatccatagt atgtaagaac acaggacaca cacacacaca cacacacaca 240  
cacacggctt attaataatg taatgttaaa taatacaatg cagggcattt acattgaatg 300  
acggttttgt ttacagcaga tttgctgggt cagaaggagc cagttgatcc acttaaaacta 360  
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<210> 57  
<211> 651  
<212> DNA  
<213> Homo sapiens

<400> 57

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attgagaatt gttgatgtag gttatctggg cagccacca acaccataca ccaccacctg    180
aatgcagtgc tgccattgca tttatatatta tactcatatt tgtaacaaat aatctagtaa    240
cacaatgata ttttaactttt catgtttcag taagtataac tggtatcat taagctgctc    300
tgttctatta tcagaacgac agatttacia aggcagcctt ttattcatgt tgagttattt    360
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atTTTTggag gaataacact ggagtttaac aaatgacttt ttaaaaaatta gacttgcaat    480
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aacagagaca gacatgaaat gaaaacgacg aaattgtggc aggtgaagtt ccaatgacct    600
tggaatatgt taccagtaat acttcacaat atataccaag tgatgggaaa a          651

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<210> 58
<211> 533
<212> DNA
<213> Homo sapiens

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<400> 58
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tttcatcaac ttctccataa tgccatacat gcatacaaat cacactttca gttattcact    180
gtagaaatct catcaataag aaatcccttg tgataactgg gccttcattg gctttctttt    240
attggccaaa tgctgagtat ttttggttg agatgataac tttattttta gcctgagaga    300
gcaggtgact tgcccttggt ctaatgatac taagcagctg ccacagcctg tttcacatcc    360
actggagaag actgttcctt ggagagggag cacataactg tgcatgtctc tttcaagatg    420
tctctttggg taccatgttg ggaagtgact ttccaagggt gaggagtgcc ctgtgtttag    480
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<210> 59
<211> 680
<212> DNA
<213> Homo sapiens

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<400> 59
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ccaaatgaaa tgggtctaatt cacaacata ttgttttcaa gaaataccag aacttttctc    180
tgactgacta aagggttatta aaaatgtttg ttctaaaatc atttctaatt tttgatttaa    240
gatgtctggt ctctcccttc cttctttga taaataaggc tgctacattt cctaattttt    300
ctagatgttt acgcaatata ataatgataa aatctaaata atggacgaca aaaaattaat    360

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gttacaaaag gaaaatattc attctttttt gtatattttt atgatgatta gggtttctaa 420  
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 ttgctgataa caccagaaga cccctacatt ctctactcaa taggagagct aatgagggtgg 540  
 catgtgatgt agatccatag tatgtaagaa cacagacaca cacacacaca cacacacaca 600  
 cacacggggtt attaataatg taatgttaaa taatacaatg cagggcattt acattgaatg 660  
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<210> 60  
 <211> 461  
 <212> DNA  
 <213> Homo sapiens

<400> 60  
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 cgatgtagag ttgccgtagt ccttcaattt gtaaaatatg caatgtctat gaagcacaat 180  
 aaagcaaagt gcaagtaaac aaagtacgcc tgtaagtgtc gatatagtaa gcttaaattt 240  
 tcattatcac cacccttgc caggtttgta gtttttgtct ttataatata gtctgtatat 300  
 gaaacaaagt aaaatctgtt ttattttetta taaagcttcc ccagagtatc tagtataatt 360  
 ctgtgcatgt agaagacttc tcagtaatta tccactactc aagagacaac ctgctgtgtg 420  
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<210> 61  
 <211> 659  
 <212> DNA  
 <213> Homo sapiens

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 ttgatactta aaaatagtag agtatgcaga ttactggaat agtgaaaatt gataacgcaa 180  
 tccctagtag aaagaaaatc cgaaagagtt ctgtataccg gctttcagta catttaaata 240  
 tatatatgtt tgaacaattc atctttatcc ctaatacaat aacttttcaa aagctaattt 300  
 ataaatgtca gtttgtacag atacaaactg tataatatcc aatataatca gatattctca 360  
 gaatatacag attaaatata cagaaataaa tgtatggta ttgcctgata ataattcctt 420  
 agggaaggca ataattcaca atttatgtac ccacagtggc agtgtagaga ggtggttttg 480  
 ccagtgatta ctttaacta agttgccaac acagtactta aaaccttcat ttatgagagt 540  
 ctaagagatc tccttcctgg aaattatcaa gtatgcatcg aggctacaca atagaaagaa 600  
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<210> 62  
 <211> 649  
 <212> DNA  
 <213> Homo sapiens

<400> 62  
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 agtaagttagc aaaaataatt gctttctatt atgtagctat acagagatga gacagttcct 180  
 acttccttaa ttcttaaagg agcagaagag tatggcacca ggaatagaac ttggggcaca 240  
 gcaggttcct ttctactgca gaaaaaggcc attctgaagc cacttatagt tacttctgtc 300  
 tccagagacc ttttctgtgc atatgaggtc aaggtagtg tccatggagc ctggaaggct 360  
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 ggggagctgg gtagggtatg atgctgggca tgttctactgt ggctagttag ttctggggta 480  
 caggcatcca aatgctcag gtgcacatca cagaagggaa aaggaaagaa aatctcggtc 540  
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 aaaaagacca ccgagtgttt gtcccttttt gtgggctcgg gggaaatgc 649

<210> 63  
 <211> 653  
 <212> DNA  
 <213> Homo sapiens

<400> 63  
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 agtgattagt tatattgact gcatgcactt ttataggagg cgatataaac agcacttcct 240  
 catctctact gtcttctctc caaaaaacct taccacagc taatcatgag aaaaccatga 300  
 gacaaaaata ccaactaaaa gccattctat aaaatacttg tccagtaatc ctcaaaaatg 360  
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 agggaaaacc tggggaatta caaataaact atggacttaa gttgacaata atgtatcaag 540  
 atcagtttta ttaattgtga tcagtgtacc aggataaagt tttaaaaata gatcagggca 600  
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<210> 64  
 <211> 574  
 <212> DNA  
 <213> Homo sapiens

<400> 64

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 gttgccaaaca aattaacata aacttgtag cctaaaacaa cagaaattta ctctctcata 180  
 gtttgagac caaaatcaag gtggtggcag ggctgcatcc tctccaaagg ctccattcct 240  
 tgcttctttc agcttctgat ggctccacat atcccttggc ttgtggctac atcactttca 300  
 tatctacctt ggtggtctca tggccttctg ctcttctagg tgtgactctt ctctgtgtct 360  
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<210> 65  
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 <212> DNA  
 <213> Homo sapiens

<400> 65  
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 acctagatta ttacgaaac ctgcaatagt tatcatttaa tgttactttc ctgtcaacca 180  
 ttttatagct tgtggatttc aggtgtttac cctaagttag aaccttaagt ttagatacat 240  
 gattatttta caaaataatt caagttttag ctattttcat taaaccaata ttaatgtctt 300  
 atttatcaaa aattacacaa gcaaaggcca tttctgtttt ggtctgggtt tatattttta 360  
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 tcttgactcc agaaaaggga gttttacaga gaaacaaact ttggatgtca actaaattgg 480  
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 tgatttgagc cataaaga 558

<210> 66  
 <211> 277  
 <212> DNA  
 <213> Homo sapiens

<400> 66  
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 gatctaataga gaaaagcggc attaacattt tcttgcaaact ctccaatgtc tagcttagta 180  
 gtagagagct gagttctcgc atctgataca ttctattctt gcaatatgtt gttttggtg 240  
 aaatatgtga caaaaatctg gtctcacaca gacatat 277

<210> 67  
 <211> 639  
 <212> DNA  
 <213> Homo sapiens

<400> 67  
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 gtggagtacc tttcctgcac cggagatgtt ccaccattac atcactatgt tgtattttac 240  
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 aaaggttgac aacagagaca acataaattt tgggcagag 639

<210> 68  
 <211> 585  
 <212> DNA  
 <213> Homo sapiens

<400> 68  
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 tgtgagtact ctacttttga tctgcatttg gttgaaaaaa atctgtgtat aaatggaccc 540  
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<210> 69  
 <211> 623  
 <212> DNA  
 <213> Homo sapiens

<400> 69  
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 aaagttaacc ccttgcttaa aaaagaaagg aaaagaaaag aggagagggg aggggagggg 120



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aggggagacc aaaattcagc caaaattaac tccttgctta aaaaagaaaa aaaaaaggag 180
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atcattgttc agaataataat tcaaaattat tcaacatatg aaaaaacaag aaaaatctaa 300
cccatattca agagaaaaaca caaccaatgg agaaaaatcc agattttttt tagtagcaaa 360
aatctgtaag caattattgt aagcagctta aggacataaa ggaaaatgtg ctcacaatga 420
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aaagatggga tctcactgtg ttg 623

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<210> 70
<211> 671
<212> DNA
<213> Homo sapiens

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<400> 70
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ccaacttgac ttcaattgca cccaacactt tgctttttta caactttccc ttcttgcttt 240
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gccaaaatta tataaaacta ttagttttta taatgtccat gtatttgctt ttaccggaga 420
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tacctggggg tgcatttatt ttgcctaata ttaacagga cagttttgct aaatacagaa 600
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cttctggcct g 671

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<210> 71
<211> 636
<212> DNA
<213> Homo sapiens

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<400> 71
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aaataatttt ccaggaatat ccccaaagtt tttgggctgg tatatcatat aatttctttc 180
agtaattgtg tggaaaaata ctttataaat gcatagatat agatagatat tttcatataa 240

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tacatgcagt gatgatctga tgagaaaaat gatgtaccct gaatgtttta tcttttaata 300  
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ttaaagaaag acaaaaggcc ttcacacaag tgattcttcc taaaattgaa aggttaccag 540  
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aacaattata tgtgtgtgta gtgtgtgtgt gtgtgt 636

<210> 72  
<211> 658  
<212> DNA  
<213> Homo sapiens

<400> 72  
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<210> 73  
<211> 405  
<212> DNA  
<213> Homo sapiens

<400> 73  
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aacagcctcc cccagccctg agtgactga tgtccgcagc gctgccctac tgtgtcagtg 180  
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gtggaggaca gacccacca gccagctagg aggggatctg gggtcctgtt ctggggaggg 360  
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<210> 74  
<211> 660  
<212> DNA  
<213> Homo sapiens

<400> 74  
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gccataaaat atgctatgag tccatgtaca gaatattatc agactggttg tgttattgca 180  
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aattcctcct tgaaagtgc cactaaaaat ttcggaagat tactaaaatg aagttgattg 420  
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tgtttcttcc aattatctta aaaatccaat cctgaatttc tagtaaatta attttaattg 600  
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<210> 75  
<211> 293  
<212> DNA  
<213> Homo sapiens

<400> 75  
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aatcctggaa atatctgaca gatgccctgc ttgaaggata agcttattag aaaataaatt 180  
acaactacta aagaacaaca aatgtttctt gggtttttgga tagtatggat tggtagagag 240  
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<210> 76  
<211> 487  
<212> DNA  
<213> Homo sapiens

<400> 76  
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<210> 77  
<211> 654  
<212> DNA  
<213> Homo sapiens

<400> 77  
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tggggagagc tttgcagctt ctgttaaatac atgaaactag ttttaattta agctcagtc 180  
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catgggcctc ctttaaacta ttttactttt agttgtccta cattatagaa agctaccaga 480  
agatttagtt tatgcatata caattaaaat acaaatacaa atatatgtat gtctgtgtct 540  
ctacatagac ctacatttat tagtcaaaca ataaaagaaa attgtttcca gttataaaat 600  
gctcaagcca aatttgtcac acagtcaagg gcttactttg ttctttgaat catc 654

<210> 78  
<211> 531  
<212> DNA  
<213> Homo sapiens

<400> 78  
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<210> 79  
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<212> DNA  
<213> Homo sapiens

<400> 79  
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aaaaaactc tttttgtaga atctacaaag ggacattttg gagtgcatta aggcctataa 180  
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tttgtgtaga atctacaaaa agacgtttca gagcccattg tggcctatag tgaaaaactg 360  
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<210> 80  
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<212> DNA  
<213> Homo sapiens

<400> 80  
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<210> 81  
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<212> DNA  
<213> Homo sapiens

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acataaaaga aaacagagac ttagtctcaa ctccatcaca tatttattaa ttcatgcagc 240  
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<210> 82  
 <211> 479  
 <212> DNA  
 <213> Homo sapiens

<400> 82  
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<210> 83  
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 <212> DNA  
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<400> 83  
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<210> 84  
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 <212> DNA  
 <213> Homo sapiens

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 ggttacagtg acagatactc ttttttcata aaccctgtgg gaagaccaa atccatctcc 660  
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<210> 85  
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 <212> DNA  
 <213> Homo sapiens

<400> 85  
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<210> 86  
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 <212> DNA  
 <213> Homo sapiens

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 <213> Homo sapiens

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<210> 88  
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 <212> DNA  
 <213> Homo sapiens

<400> 88  
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 <212> DNA  
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<210> 95  
 <211> 518  
 <212> DNA  
 <213> Homo sapiens

<400> 95  
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 attatcttaa aaatcctcaa atagtttacc attctcaaat accaactga aatttcactt 180  
 tactacaaag cctccaatc gccagcagct ctccatcatg cttaagttca cttctttcta 240  
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 gggcaattgc tccattgggc tcccttcata tttctcatat cttaacagcc ttattgtac 360  
 ttttttctt ttgagtttac taaaaatggc tcatattctg taccocatgc aaaaattctc 420  
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 actttttata cttcacatgt ctccattttc ttatctgc 518

<210> 96  
 <211> 717  
 <212> DNA  
 <213> Homo sapiens

<400> 96  
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actgacttcc acagccacct ctttcttgcc tgcttcatgc ttgtgtcac acagagctcc	240
atcttcagcc tctgtccat ggccatcaac aggtacctgg ccagccacag tcggctcagg	300
cataaaagtt tagtacttg gacccaaaca agaggggtta ctgctgtcct ctgggtcctt	360
gcctttggca ctggactgac cccattcctg gagtggaca gtaaagacag tacctctaatt	420
aactgcatgg agccctggga tggaacctg aatgaaagct gctgccttgt gaagtgtctc	480
tttcagaatg cggtagccat gaggtagatg gtatatttca gttttggggg gtaagtcttg	540
ccccactgc tcgtaatgtg gctgatctcc atcaagttct tcacagtgc tgcaggcagc	600
tttagtacac ggagctgatg gaccactcaa ggaccaccct ccagtgggag atatacacag	660
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<210> 97  
 <211> 650  
 <212> DNA  
 <213> Homo sapiens

<400> 97	
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attatagagt tttttcatag aaaggatgga tagatacaag tttttcctaa caagcacaag	180
tggcagtctt tgaaaactaa ttttttatgt gtacattgta gcattggaag ataactgtgg	240
ttgagtgtga taaactgaaa ctttttaaaa aatctattat tttttttaca agttaagtta	300
gagccagata tgctgattct ctaccatttt caaaagagga attggaaaag ggagagcttg	360
tttatgtggt attcacaata gtgtctgctc ctgaagaaaa tttttggaaa aatctcatga	420
gtgtcctcag actgaaaaca gggatccagt ctgttggttca tgcaggactc aggaggcgag	480
cgagcatgtg ataccaggaa gggtagcatc cctgcctctg tggggagccc tcagtggcga	540
ggtggcgagt tcaggcttca cttcagagca tggatactgc tgcataagtg ctggaagggt	600
gctgcatggg tgctggaagc tgcttgcat agtgcatgtc ctgtttcctg	650

<210> 98  
 <211> 611  
 <212> DNA  
 <213> Homo sapiens

<400> 98	
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gcaggcagag acactatgca tacagatacc ataataatag taaagaatgg ttgagtggag	180
aaccagtgcc tctgttccaa ttatttttat aattgctctc tatctactat ctctacagat	240
attccataaa cagtgtgcaa cactaactcc atcctttcgt tgcatttggt attatttttg	300

ctatagacaa aattttcaac catgcagaaa caaaagttaa aaaccgttac attgttctct 360  
gcatttacag gtttgagta atgtagggtta attagacatg ctgttaaag accaaattaa 420  
acacatcatg ttttggtaaa gaaacgaacc caagaagtag taaagatggt ggggaattcc 480  
tgaatcccaa aagccttctt aattttgacc attggacatt catatatgtg tgtgtgtgta 540  
gtaattcaaa tcagaaaaac aaccaaagg ggccagctct caaaatccag gcactttagt 600  
gagacaaagg c 611

<210> 99  
<211> 598  
<212> DNA  
<213> Homo sapiens

<400> 99  
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attcttcctg gattgtgttt ttttaattat ttttctgtg ttgtcactga gcccttccat 120  
gtctccgaaa ttcacacctt ccatgctttc acaataagag tctggccagt catggcccca 180  
caaattctat acaccatacc cttgttggtt cattttatca acttatttgt ctatttcaag 240  
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ccaagtagcc aagactggaa gcagtcacca tagggcaccc ccacagtttg ggagggtgtg 420  
cagacaaagt tatgggatac ttagtcacca caaaactctg gcttgaaact tgtctccttc 480  
ctccccaag ttctcagga atgtatagtc actgtcactg ctgggtttac ttctgttatt 540  
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<210> 100  
<211> 576  
<212> DNA  
<213> Homo sapiens

<400> 100  
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acaaagagcc agaactttta tatttagaaa aaaaatgtg cccaggatgt ataattcaca 180  
ttaaagcca tttgttgaaa gccataaat acatatatat gtctagtga caactcacag 240  
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ggctctcaaa tgaagaaatg ccgtccgtca agggcataca tattcgga tgaggagcat 480  
aggagcagta tcgaaagttt ttgaaataac taaagtcaaa gggaaaaaaa gtgtcacttt 540  
gcagcaatga tacagaacct acagttgcag tcctat 576

<210> 101  
 <211> 657  
 <212> DNA  
 <213> Homo sapiens

<400> 101  
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 tggctgtgtg ctctgtgctc acccacctgt gaatcacccg gtggtacaga gtgacaatcc 180  
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 cctgtgggga tggctggcat tctggatatg ttggaaacag cactgggttag acatggagca 360  
 atgtccaagt gccagcccca ctcatctgct acacgtgctg tgctattctg cttcactcgc 420  
 aaaaaactag actgcagcgc aatataccgg ctcatccttg tgtggttctc cagcactcac 480  
 gggcaattat ttctccatth ctatgtgtth taaacctgtt ttctctccga cctgtcaatg 540  
 agagcatgaa cctttatgaa cccacactcc ctggaccctc ttgatagggt tcgtggaagt 600  
 ggaatcattc taagaagcag tgaaggcagg gtgctgttht ctgctttcac agctctg 657

<210> 102  
 <211> 547  
 <212> DNA  
 <213> Homo sapiens

<400> 102  
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 ccacatccag tatactacag aaagagtgtt tcaaacctgc tctatgaaag ggaatcttca 180  
 actctatgag ttgaatgcag acatcagaaa gaaatthtctg agaatgctgc tgtctacctt 240  
 ttatttgaat tcccgtthc aacgaaatcc tccaagctat ccaaatatcc acttgcagat 300  
 tccacaaaaa gagtgtthtca aaactgctct ctatcaatgg caaagttcaa ctctgttagt 360  
 tgaggacaca taccaccaac aagthtctga gaatgcttct gtctattht tatgggaaga 420  
 tathctctt ttcaccgtag gcgtcaaggc gatcgaaatg tccacttcca caaactacaa 480  
 aaagagtgtt tcaaacctgc tctatgaaag gccatgttca tctctatgag ttgaatggaa 540  
 atatccg 547

<210> 103  
 <211> 762  
 <212> DNA  
 <213> Homo sapiens

<400> 103  
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tctgtcattt agcagaagta gcctggagtt caattcttca aataactgga agctgtgatg 240
tctctggagt gacctgtcct gcatcaagct gtgtcttgga ggtagcacag ggacctgaga 300
caacatagag tgaactgctg gctcaagccc cctgttacac tgggtctgca atactgcca 360
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acaaacaaat ataatgaaaa gtagccaaca aactgaacaa gtaggaaaat taattcttga 600
agcacttcaa ataatagagc aaagcctgaa ctgaacttaa atgaagtata ttgtattcct 660
cagagataaa ggtggttaata acacctataa agcaagcata agaaatcatg agccaaaaaa 720
caagagtcaa aaaggcttgg gaagtttggg tgtggtggca ga 762

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<210> 104
<211> 515
<212> DNA
<213> Homo sapiens

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<400> 104
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aggtgggttt cagacattat aaaatctggt gatgtaaaaa ctaagaaaac aaataagatc 180
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ttgctccttt tcttttccca tctgcctgag gctattataa aaaaatatta aggaacatta 300
ttgctaatacc ataataaatg gtacattaac tatgatccaa cttatctttt ctacacaagg 360
gccacgggac tgcattgtga taaaatctgg actggattta tttttttagg ggcctgatcc 420
catgtccaat cattaacctt taaggagggt cttaaaaata attttattat taagaagttg 480
aatcatcata attatagtat ccctctgact tcaaa 515

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<210> 105
<211> 344
<212> DNA
<213> Homo sapiens

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<400> 105
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ttttttaaat gacatttatt tctgggtttt cacacatgtg ctttacatgt tcttgttttc 180
ctttacaatt gaacatacac tctatcagcc agaggccagt gagcatttga tgggggcca 240

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aaataaaaaa aaaacgagtt ttggcatagc taatactttt catctttgcc tcatccatat 300  
 taagtttgag tcttgggctt attattaatt tgagcacttt catt 344

<210> 106  
 <211> 453  
 <212> DNA  
 <213> Homo sapiens

<400> 106  
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 taattccact cataggtatt catctcagag taagtaaaag cggtagtcca ttaagaaact 120  
 tggataagaa agttcacagt aagctttatt caaaagaccc caaaactgat aacaacccaa 180  
 atgttcacca cccagagaat gaataaacia atcattctgc attcttaaac aaaacaaaaa 240  
 caaaacaaaa cactccatg gcaaacaaaa ggagaaaatg cctgatacac acaacagcat 300  
 gggatgaatat caagaacatt tgctgagtga aggtacagtt atacagtagc gcattctgta 360  
 tgggtccaca tacacagagt tctagaatat ataaaaaaaa aactattcta aaaaaggaaa 420  
 taaaaacagt tgtattgttt ggggaggtgg gga 453

<210> 107  
 <211> 335  
 <212> DNA  
 <213> Homo sapiens

<400> 107  
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 tcatggcaca gacgatgctg aggccggact gactgaagaa gaacaggctg aagatgctgt 120  
 actcacacag cagctggccc ccagggtacc cgcccttcac gtacatggcg atggtcacct 180  
 ggctcaccag caaagtgaac aacaggctgg tggcagccag ccgcataact gtgtagaagg 240  
 tggctcctt ctgctccttg cgcgacttgc acagcaccac gatggccacc aggttgccca 300  
 ccaccccgaa aatggacggg tcccaagctg tccag 335

<210> 108  
 <211> 573  
 <212> DNA  
 <213> Homo sapiens

<400> 108  
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 ttccagaaga aaattgctaa atatgccaaag gtgtcatatt atttttttcc cagcatatta 180  
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 tcgcttaaca gagccaaatt cagcccagag tgagtctttg gtgtccatcc caggctctgg 300  
 ctaccatgtc acccagacgg cctgatttga aggcagtttc cttcccaggg accacggcag 360



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agtgccacaa gattagcaga gagtctcgtc tccagcttgt tgacgtacgc tacaggtctt 420
gggattttgcc agcatcttat aattttgtac aataaatgaa gcacccatgc agtgcacaca 480
cacacgtaca catgctatta attctatgag tcttgggact tgccagtctc tttttttttt 540
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<210> 109
<211> 663
<212> DNA
<213> Homo sapiens

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<400> 109
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taggaaaagg agcctgagac agattgataa gatattaaac aaggctgaaa atgaaaaaaaa 180
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gttctaagtt tctcatatg gcccttagca ccacatcaac acaggagagc acatcataaa 420
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gctcgaaaaa cactgtaaaa gctgcctctt taataaggat cctggtgtcc cgtgatggat 600
gctataaaac ctcagactgg ctggtgtgct cacagccatg taggaccatt aacagcgtct 660
ggt 663

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<210> 110
<211> 590
<212> DNA
<213> Homo sapiens

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<400> 110
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taatcacatg aggaggaaga taatgggaca aacaactggc ttcaggattt ttttttcttt 180
tctgagattc acaccaaatt tctgcatgct tgagatttac tttacctaaa attttttaggc 240
ccaaaatcag tagaaactca attgactgtt ttgggggacc ttgtctgtcg acagtgtatt 300
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tttggttggc attctttcct ctacctaat ctgtaaagat cagatagtat ttgttctaga 540
gataaacttt ttcttttctc atacacacac tcagtacaca agaagcccac 590

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<210> 111  
 <211> 651  
 <212> DNA  
 <213> Homo sapiens

<400> 111  
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 gaaccgtggc cgagggtgaaa ctgagggttag cccagcacag gttggagagg aagaagtaca 240  
 tgggggtgtg gaggtgggag tcagggttga cagccaggat gatgagcagg ttcctcagca 300  
 ccgtgaccag atacatggac agggacaggg acagcaaagc aaggaccggc tgcagttctg 360  
 gatccctga gaggccagg agggaggaatt ctgagacacc tgtgagactc cgtggctctg 420  
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 gccagcaatg tttctcagtt gtgacaaatc caaaaatctc agaattgtta catgttttac 600  
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<210> 112  
 <211> 623  
 <212> DNA  
 <213> Homo sapiens

<400> 112  
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 atagtggtag tgtgggtctcc atgattgttt gatgtaatg atcaacaatg ttatccagga 180  
 cctgggttca tgctttctcg ccatttcgct atcttttagtt ctggattcat atcaagatgg 240  
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 gaaccaatta ttgtcatgac aaatgaagta tccttggaac atgaaacaca ttgctgaaac 420  
 tgggttagaa cttcccccaa ggcacaaaga taaagagggg aaggtagat agctaaacaa 480  
 atctgtttct agtataagtg gaaaagggga gaatggatac ttggtagaca aaccatagtg 540  
 tccattacta aaagatactt gagggacaat gtacagtga ttaaagtgat acaattgcta 600  
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<210> 113  
 <211> 605  
 <212> DNA  
 <213> Homo sapiens

<210> 111  
 <211> 651  
 <212> DNA  
 <213> Homo sapiens

<400> 111  
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 tcaggcagcc cgcattgagag atgactctgc tatgcaactg catgtccaca gtcattcttg 180  
 gaaccgtggc cgagggtgaaa ctgagggttag ccagcacag gttggagagg aagaagtaca 240  
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 gccagcaatg tttctcagtt gtgacaaatc caaaaatctc agaattgtta catgttttac 600  
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<210> 112  
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 <212> DNA  
 <213> Homo sapiens

<400> 112  
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 atagtggtag tgtggtctcc atgattgttt gatgtaatag atcaacaatg ttatccagga 180  
 cctgggttca tgctttctcg ccatttcgct atcttttagtt ctggattcat atcaagatgg 240  
 ctacagcact ttacagcaatc ataccatgct tgacactaac tagggaagaa tagagaatgt 300  
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 atctgtttct agtataagtg gaaaagggga gaatggatac ttggtagaca aaccatagtg 540  
 tccattacta aaagatactt gagggacaat gtacagtga ttaaagtgat acaattgcta 600  
 atgggttgag taattacaca ttt 623

<210> 113  
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 <212> DNA  
 <213> Homo sapiens

<400> 113  
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ttatatctta caattaagaa gttttaaaaa gaagactatt tactggcaag gaaagcatat 180  
tcttgaagta ttatgaaatg aaaaaagttt acaaaaccat ttatatggtg tgatctcaat 240  
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aaacatccag gtaaaatggt agtaatccct ggggtgcaagc acaagtgttt ttgtttgttt 360  
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aatagaaaac tgagaaagag attcagtaga tgtaagaatt tgatgtgtga taaagggggg 540  
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<210> 114  
<211> 707  
<212> DNA  
<213> Homo sapiens

<400> 114  
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aatctaagt agtcttaaaa accagaattc ctcttcccca aggtaggta taaaaacttg 180  
aaccctctta ccccaaatca aatcataaaa cctataaatg tcacactct cttctccct 240  
taagaccctt attagatgca ggtcctcccc tatacttggg aaaaaggcat cttcacaga 300  
gaaatcaaga agtatctgaa cagagaggcc tgctggtgtc cccctgctg tggtttggat 360  
atggtttgtt tggccccact gagtcttatg ttgaaatttg attccaatgt tgcaagtggg 420  
gtgtggttaag agatgttttg gccatgaggg tggatccctc atgagtgact tggttccatt 480  
ctcacaggag tgagttctca ctcttagctc ccaaaacaac tgtttgttga aaagagcctg 540  
ataccgcctc ctctctccct cttgcttcct gtctggtgt gtgacctctg tacacttcgg 600  
gttccctttg cttcttgccg tgagtagaag cagcctgacg ctcttgccag agcagatgct 660  
agtgtatgc ttctggcatg gccagcagaa ctgtgagcca cattttc 707

<210> 115  
<211> 681  
<212> DNA  
<213> Homo sapiens

<400> 115  
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tgccttcata atccccagaa gtctgtctgt tcatgctccc tgggattccg ttcagaaaac 120

aagtaaattgg tgccttctgc acattttatgt taaacggaga accaaaaaga gtgactaccc 180  
 cactccagtg cttgctgggg ctgggagaac aaagaagctg caagtatgag gtactcaaag 240  
 acagtgttac tagggtaatg attttccagt atggccaaaa gacatcttct atgcaaccaa 300  
 gcctcacctg gccttacaaa acaaaagtgg tttggccaga gcttgaataa cagctgggat 360  
 ggatggccca atgtaaagga gcaggtggca ggccagtga cccactctg ggggtggccc 420  
 atgggtggaca gagcccctgc tccctaaaat ggccaacacc tgtcccaagg aaggccacct 480  
 agccagaagt gccaccatc tgctgtaatc aaatttgcaa tcacaggtaa cttttcctct 540  
 caaggggtcca gctggcaata taaataaatg gaatgaatgg ggctcctcag atgagtacag 600  
 catcttccat gtatggggag cagacattac tgagctgctg ccatgtggga atctcagtc 660  
 agttgtgcca ggtcttctga g 681

<210> 116  
 <211> 678  
 <212> DNA  
 <213> Homo sapiens

<400> 116  
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 tgtcaagtga atttctggac tgttgtctga attcgtttgt tagggctccc attacaaaat 120  
 accacagact ggggtgactta tacaacatga atttattttc acaaattctg gagtctggat 180  
 gttcatgatc aagggtgtcg caggtttggg ttcttctgag gcctctctcc ttggctcaca 240  
 gaaggacgtc ttcttgctgt gtcttcacat ggctgtccct ctgtgtgtgt ttgtgtccta 300  
 atctcctctt cttataagga cacctgttat gctccatcag ggcccatctt aatgactcca 360  
 ttttaactta attagctctt taaagatatt ttctccaaat acagacacat tttaaagtac 420  
 tgaggaggcg ttttaacttt atgaatttta ggggggacac aaatcagctt ataacataac 480  
 aatgttatgt ttaacataac aagtttaaca aaacttgcaa aaacatcttt cagatacttt 540  
 catattaaaa ttttcttctg gcagtgattg atcctaagta ctctgaacta ttgacatttt 600  
 aactaatttg atggctaggt cctcattata ttagtttatt gccatctctt tgtagacatc 660  
 aaagcagcaa aaaaggaa 678

<210> 117  
 <211> 697  
 <212> DNA  
 <213> Homo sapiens

<400> 117  
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 tctttgagtc agtggttgaa tgctctcac accagagggt gaggtcttgg aaggaggaa 120  
 ctgcagttgg taggctctgg gtcaaggaga cctggattca agtctgcct ctctaactta 180  
 ctggctttgg gcaaattact taacctggct gagccttggg ttcctcatct gtgaaatgca 240

gttgctgtga ggatttgatg agccaatgca catgagactt gaggagtact ggctgtgaat 300  
gcaaggggttg cccttggtgc tctctcttca tccctggagc ctggccctgt gcagggctgg 360  
gaggatgcag gtgcttgga gatgggcttg gctaattgga gtcgctgtgg cttttgcaga 420  
tgaatatgaa tgccaggcct gccgaataa cgagtgggtcc taccagagtg agacctcctg 480  
cttcaagcgg cagctgggtct tcctggaatg gcatgaggca cccaccatcg ctgtggccct 540  
gctggccgcc ctgggcttcc tcagcacctt ggccatcctg gtgatattct ggaggcactt 600  
ccagacaccc atagtctgct cggtggggg ccccatgtgc ttctgatgc tgacactgct 660  
gctgggtggca tacatgggtg tcccgggtga cgtgggg 697

<210> 118  
<211> 673  
<212> DNA  
<213> Homo sapiens

<400> 118  
atgtgtatat atatataaaa aaggtaatat aaaatatatg taatataaat atatgtaaaa 60  
tattaaatat acataaaatg tatgtaaaat ataaaaatat ataaaatata tgtaaaatat 120  
aaaatatatg taatatttat actataaaaa tatatataaa tgcaggggtt taaaatcata 180  
tttatatgat atatatgtaa aatcatatat gtgtgtgtgt gtatatatac atatatgatt 240  
ttaaaccct gcatttttta tattattgga gtagaaccaa tccttttggt gataactaaa 300  
agctagccac ggatacattt gcctagattt tttgatttat ttgtgagctg ccaaggatgg 360  
caacaacttc aagactttct ttggcaataa aacatagtca acatatttaa ataaacaaac 420  
atttaaataa atataccgta aagtataatt aaacattctt taaaatgaaa acacttgatt 480  
aaaattattc ctaaatggag tatcaagatt ttgatactta taagagatta tgggtgtctgt 540  
gaaagaattg ataaatagat caatagaagt caagaaagtg gttacttttg gagaaggat 600  
acagtgggga ttttgattgc taccaatgtc caatttcttg accctgtgtg atagtaaadc 660  
atttgactct aca 673

<210> 119  
<211> 495  
<212> DNA  
<213> Homo sapiens

<400> 119  
cacacacctt cttcgttgct tgaaccctgc aaaaaacatt cataaaacta ttagatttag 60  
ataacatatt tcaaataagg ttattcttta attcaattca ttttactga atactatttg 120  
ccaaaaacag tggtaaatac tgaagatata aagatgagta agttcttgta ctcaagaagc 180  
ttatggtcta gtaaaaaaaaa aatgcagtc atgcaaaca ataaagacaa aaggatatca 240  
aatgtgaaac aatacataca gagctttaca cagaaatatg tagtcattac aaggagagtt 300

ggaaaatgct ttaaaacaag gtaatagctg atctgagttt tgaaagctga gcacgtcttt 360  
 agcaagaaag caagcataat agatgactca aaagccaaaa tgttactatc cgagtgcacat 420  
 ggattgctgt tataagatag gtagaatcta aaaattgtgt ttatgtgtgt ctaaaatatg 480  
 tctctgcgtt gcact 495

<210> 120  
 <211> 675  
 <212> DNA  
 <213> Homo sapiens

<400> 120  
 ctctggagc ctggactcac atacatcacc atgactgagc catagaagaa agaaacaacc 60  
 aagaaatggg aagcacatgt agagaaagct ttgttctctgc ctgagccagc tgggacccac 120  
 agaacagctc gcaaaactaa gatatgggac ccaagaatgt agaggaaggt gatgaagatg 180  
 atgagagagc ttactgtagc acaagtcaga gtagtttttg gaactggggc acaggacagt 240  
 gccagcaatg gtcccagggt acagaaaaaa tggtcagtga tgttagggcc acagaaaggc 300  
 actcgggaca taagcactgc aggcacagc atggatagaa aaccacctgc cctgcagaag 360  
 gccactaatc ggacacacag gtggtgagtc atgactgtgg gataatgaa aggtcgacag 420  
 atggtaagga accgatcaaa ggacatcaca gacagaaagt agccttctgc agcacacatg 480  
 gagaagtaga agaactggag caggcagcca gcataggaga tgctcttgat atgggagatg 540  
 agattggcca acattttggg acatcagaac taatgcagca gatctccagg aaagagaaat 600  
 tagccaagag gatgtacata ggtgtgtgga gtttctggct tgaccacaca gcgcagatga 660  
 tggatgtgtt accca 675

<210> 121  
 <211> 572  
 <212> DNA  
 <213> Homo sapiens

<400> 121  
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 tctgccagga tttctttctg gaactccctg tggctccagt tgccggattt cagagattgc 180  
 tgtggggaat gccatggaat agaactctggc caccttgagc tgagaaaggt gtttgtgatt 240  
 gatggttgat gccaccaagc aaacagggtt aagcaacttg actgcctgcc tgctgctttt 300  
 aaaaaggcag ctgacgacct aattctgttt agaattaggg gcgaagctaa ggaaactggc 360  
 tcaggctgtg agtatcatct ctagattcag atttctggga ccacatcaga aaccaggttt 420  
 tatgtggacc tttgatgggc agtgtggtgt gcaacgtggg ggactgtggg ttttagactg 480  
 ggcagttctg gctggggatt ccagttctac cccttagcag cattgttggg aggacgaaag 540  
 ggaaatgccg gatgggaagt gcaagatgca gc 572

<210> 122  
<211> 600  
<212> DNA  
<213> Homo sapiens

<400> 122  
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tcgttattca gatgataaaa gcctcttcct tctctatttt tccatttgca ccatcacacc 120  
aggggaaatt atggagatga gaaatactac ccagactttt attctcctgg gactctttaa 180  
ccacaccaga gccaccaag tcctcttcat gatggttctg agtatcgttt tgacctccct 240  
gtttggcaat tcctcatga ttctcctgat tcaccgggac cggccggctc cacacgcca 300  
tgtacttcct cctgagccaa ctctccctca tggacgtgat gctggtttcc accactgtgc 360  
ccaaaatggc ggctgactac ttgaccggaa ataaggccat ctcccgcgct ggctgtggtg 420  
tgcagatctt ctctctgctc accctgggtg gtggagagtg ctctctctta gcagccatgg 480  
cctatgaccg ctatgcggct gtctgccacc cactccgata tcccactctc atgagctggc 540  
agctgtgcct gaggatgacc atgtcgtcct ggctcctggg tgcagctgac gggctcctgc 600

<210> 123  
<211> 662  
<212> DNA  
<213> Homo sapiens

<400> 123  
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ctcagttttt gtatttgcaa aatggcagtg ggtcagaccc cttagcctca aagggccctc 120  
ccaacctctg gcacttgagc atctctgagc ctgctgggcc acctgtccca gtgcctcttg 180  
ggcttttgaa gttgaatgct gcaaccccaa gcccagttt caggtaggga tgagcccatt 240  
gccaatgct ggggtccgag tgggcctgaa ggctcccaga ggaccacgtt ctgagccctg 300  
gatgggcagg gacctggag acctggcctg tgtggacaca ggggagtaag tactgggact 360  
gagcctgtag ttttgcttct tccaccaac ccgttggggg tcgttctcac agcttggtgc 420  
tgggtacacc aggggactca ccattggagg gatccgatgg gttccaaggt gcacaaaaca 480  
gacccccagg tcatcctcag gtggtctaca cagcctgtgg cttaaagcaac tgctgtctcc 540  
agcacttctt agcttcagtc tggtgaaagg aagaaagtcc cttgggcagt gtcttacagg 600  
cagtcataga gggacccac agcctggcca aaatgctcaa tttcagaaaa tcccagactc 660  
at 662

<210> 124  
<211> 660  
<212> DNA  
<213> Homo sapiens



<400> 124  
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agctttccaa tagggaaaac attcagtcta gtagcttggt ctgctactag actgcctcag 120  
tgaatgagta actgactgga ttaaacaaaa caccacagaa atatttacca agaaggtaag 180  
gtccaaaagg aaggtagtga aaggaaatgt actctgatca tgaaatgggt ggttgatgag 240  
caagtcaagc ttgaagattt atctcttttc ttcattcaga aaagcaactg aaatgcaaac 300  
tggtgctatt aataacatag tccttgaaga caacctaaaa atagttccta aaatgccatt 360  
tgtaactgta attttgcac tcaatcattg gcagtttga atgacagtat tttgtacagc 420  
aagatgatgc acattataat actatatata gagagagaga catgcatgtg ctctccttc 480  
ttccccacac aaatcacccg gaggtcataa aaatgtttaa gttccaccag gagtaagcaa 540  
aaatttaaca aggaaatata tactcatttt acatttaggt aattaagtag taatctcctt 600  
gatgttaatt tttatttctc caagttaaag ttcttgctta tatgaactct tgctttctaa 660

<210> 125  
<211> 680  
<212> DNA  
<213> Homo sapiens

<400> 125  
taccaagtaa aaattttaaa gccgattatt ttatttctgc tttcatgaat ttccagtgt 60  
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agagttacag acataattat aaatcaggta ggtagggag atacaagttt catttaagaa 180  
atgaactgta ggggaaggta gtgggaaga gggatcagga gaggttgcc aatgggtaca 240  
aagttacagt taggaagaat aagttctggt gttttgttgt acagtagggt gcctctggca 300  
aacaacaatg tagtgtatac ttttaagata gctagaagag aagattttga atgttatcac 360  
cactaagaaa tgatcaatgt ttaaagtagt aaatacagta atgaccatga tttgatcatc 420  
atgcaatgta tacactcatt gaaacatcac actgtacccc ataaatgtgt acaatcatta 480  
tgtcaattat aaatattaaa aattaatttt aagaagaaac gcagaaaaaa atgttaacag 540  
tgttctaaag gaaggacag ttgcatcgga aagacttga aatgtgtaag gtgacagtca 600  
agagaaatgg gagtttatgg tgaccgagta ggatatggat caaggtaacc accagcaatg 660  
ggtgtgaagc attgcatatg 680

<210> 126  
<211> 642  
<212> DNA  
<213> Homo sapiens

<400> 126  
ggctgctgc atcatttccc ttgtcacgct ggacagggaa acgcggttgt gctctggctc 60  
ctgggcttcc gcatgcgcag ggaacgccgt ctccatctac atcctcaacc tggctgcggc 120

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agacttcctc ttctcagcg gccacgttat acgttcgcc tcactcctca tcaatatctg 180
tcaccccatc tccaaaatcc tcattcctgt gatgacctt ctatacttta caggcctgag 240
ctttctgagt gccatgagca ccgagcgctg cctgtgcgtc ctgtggccca tctggtaccg 300
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ctactgcgga gcaccttgga gtgaatgttc tgtgacttcc tgtttagtga tgetgattct 420
atttggtgtc aaccatcaga ttcatcaca gtctgtggc tgattttttt atgtgtggtt 480
ctctgtgggt ccagcctggt cctgctgatt aggattctct gtggatcctg gaagatgcct 540
ctgaccgggc tgtacgtgac gatcctgctc acagtgctag tcttcctact ccgcagcctg 600
cccttcggca ttcggtgggc tctgtctact gggatacacc tg 642

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<210> 127
<211> 558
<212> DNA
<213> Homo sapiens

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<400> 127
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tcacagggt cttctaaagc atagggctca gggaaggagg gttatcaaca tctggccaag 120
ggctggagat ggaaatgttt ccagacccta aagcaagaaa aagatcagca ggtagagaa 180
aaagtaagat ggccacttac ttagagtga ttagataag aataaaagcc gtgccccagg 240
agtaggcaag aggctgatta ttgagatcct gtaacccatg ggaaggaacc ctaatcttat 300
gatgctggtg atgagaaagt gttggtggg tagagtaaga gaacacatta atctgctttg 360
cctcatggaa agaataaatt ctggtagaca tatgtagatg cagagagtga gctattatag 420
tttttgtaag agagattatg gtttgactta tgggtacagt gatggacatg gtgagcaatg 480
gatgcctttg tgatctgcag actttttacc tgacacactg agtgcattgat catgccattt 540
actgagaggt gacaatgg 558

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<210> 128
<211> 596
<212> DNA
<213> Homo sapiens

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<400> 128
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ggactgaaaa ttataggaa gaaacatttg tccttggtgt ttctgaaata tgtgaaccaa 120
acccaatgc ctgcactttt gctctcaca acttctgaca tgaggcacag atttttacaa 180
aacagcttaa catagaagtc tcacaaaatg tgcagatttc ctcagatccc aaaaacaatg 240
gaaaagcact cagaccacaa gagcttcatt ggaatagcag aaagaagagg cgaactttgg 300
ctgtcactgt gaatgcctg gaatgttagt ggatgaacag agaagcctta gaagatttaa 360
gagcataata agcatagggt aggaaatttc cacctgtggc agcaaaagaa gtaaatttag 420

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aattttccag aaccaatttc tttgaagcag aacttccaac accacatttt taagggtttt 480  
 ctcttggcc tttgcacctc tcattttgt tatttgttca ttcttccta ttgggtgtt 540  
 gcctattatt gtctctcttt ttacattcca aagaacattt cctttactgt aggaca 596

<210> 129  
 <211> 180  
 <212> PRT  
 <213> Homo sapiens

<400> 129

Leu Pro Ile Arg His Tyr Pro Ser Ala Thr Ser Ile Phe Leu Ala Tyr  
 1 5 10 15  
 Ser Ala His Phe Leu His Leu Thr Gln Asn Gln Lys Pro Leu Val Pro  
 20 25 30  
 Leu Ser Ser Pro Thr Pro Thr Ser Thr Ser Leu Leu Pro Phe Ser Gly  
 35 40 45  
 Leu Pro Phe Phe Arg Phe Ile Phe Ser His Ser Leu Trp Asn Leu Leu  
 50 55 60  
 Pro Ser Ala Phe Thr Pro Thr Gln Leu Thr Ser Phe Pro Ala His Cys  
 65 70 75 80  
 Pro Pro Leu Ala Asn Gln Pro Ala Gln Phe Ser Ser Val Phe Thr Val  
 85 90 95  
 Pro Asp Val Ser Ala Ala Ser Ser Cys Ser Leu Pro Pro Ser Trp Lys  
 100 105 110  
 His Val Leu Pro Trp Leu Pro Gly His His Ser Val Phe Phe Ser Ser  
 115 120 125  
 His Trp Leu Leu Leu Ala Ser Phe Leu Phe Ile Ala Phe His Asp Phe  
 130 135 140  
 Asp Ser Pro Trp Thr Ala Gln Gly Ser Val Leu Glu Leu Phe Leu Phe  
 145 150 155 160  
 Phe Pro His Ser Val Pro Pro Pro Leu Val Ser Trp Ser Gln Ile Pro  
 165 170 175  
 Cys Leu Pro His  
 180

<210> 130  
 <211> 186  
 <212> PRT  
 <213> Homo sapiens

<400> 130

Leu Asn Ser Glu Cys Tyr Asn Leu Cys Tyr Asn Gln Leu Ser Lys Ser  
 1 5 10 15  
 Tyr Val Tyr Thr Tyr Ala Tyr Phe Phe Cys Asp Leu Asn Leu Gly Gly  
 20 25 30  
 Gln Pro Tyr Leu Val Ile Phe Val Lys Val Thr Lys Leu Gln Tyr Ala

35                      40                      45  
 His Phe Ser Lys Cys Ser Arg Leu Leu Ile Met Leu Gly Ser Phe Ile  
     50                      55                      60  
 Ile Tyr Gly Phe Ala Lys Thr Asn Cys Lys Ile Gln Tyr Ala Leu Ser  
     65                      70                      75                      80  
 Tyr Ile Ile His Thr Tyr Ile His Ile Tyr Glu Lys Glu Arg Glu Arg  
                     85                      90                      95  
 Glu Arg Gln Arg Tyr Leu Asn Trp Asn Gln Val Lys His Ile Ser Thr  
                     100                      105                      110  
 Asp Pro Lys Phe Leu Lys Asn Ile Ser Leu Val Phe Phe Lys Pro Leu  
                     115                      120                      125  
 Val Asn Ala Thr Thr Asn Gly Tyr Ser Val Leu Phe Leu Gln Phe Ile  
                     130                      135                      140  
 Leu Leu Ser Ser Lys Leu Leu Lys Ile Phe Val Cys Leu Cys Ile Phe  
     145                      150                      155                      160  
 Ser Leu Glu Thr Ile Leu Gly Ile Leu Asn Lys Gln Pro Leu Ser Gln  
                     165                      170                      175  
 Glu Thr Leu Ser Glu Cys Trp Gly Gly Arg  
                     180                      185

<210> 131  
 <211> 144  
 <212> PRT  
 <213> Homo sapiens

<400> 131

Phe Gly Gly Leu Leu His Gly Cys Met Lys His Thr Ser Cys Lys Leu  
     1                      5                      10                      15  
 Lys Ile Asn Lys Leu Gly Leu Pro Ser Leu Gly Pro Leu Pro Phe Tyr  
                     20                      25                      30  
 Gly Ser Ser Val Phe Thr Leu Leu Asn Leu Ala Thr Val Leu Phe Trp  
                     35                      40                      45  
 Ser Val Phe Val Met Ala Gly Ala Glu Phe Ser Leu Ala Val His His  
     50                      55                      60  
 Cys Cys Leu Leu Pro Ser Gln Thr Arg Cys Leu Pro Ser Leu Ser Ile  
     65                      70                      75                      80  
 Arg Gln Ser Val Arg Cys Ala Pro Asp Pro Ala Ser Cys Pro Leu Pro  
                     85                      90                      95  
 Phe Leu Ile Gly Leu Lys Ala Cys His Cys Ser Cys Thr Ala Lys Arg  
                     100                      105                      110  
 Pro Gly Ala Ser Ser Ser Ser Ile Leu Val Thr Gly Phe Cys Gly Phe  
                     115                      120                      125  
 Ser Ser Val Thr His Gly Phe Ser Ser Asn Thr His His Met Ala Gln  
                     130                      135                      140

<210> 132  
 <211> 183

<212> PRT  
 <213> Homo sapiens

<400> 132

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Leu Gln Ile Asp Tyr Ser Ser Ile Lys Asn Cys Gln Lys His Glu Gly
1          5          10          15
Pro Lys Gly Glu Thr Asp Ile Gly Lys Ala Leu Val Val Val Glu Val
20          25          30
Gln Gly Leu Ser Pro Asp Cys Ser Ala Ser Ser His Ser Ser Leu Pro
35          40          45
Ser Arg Leu Ala Pro Ser Phe Pro Arg Ser Pro Gly Phe Ser Val Thr
50          55          60
Tyr Ser Glu Lys Tyr Cys Pro Ala Glu Leu Asn Ala Ser Ser Ser Thr
65          70          75          80
Tyr Leu Leu Gly Pro Phe Ile Phe Leu Pro Leu Ala Ser Phe His Leu
85          90          95
His His Leu Val Thr Ser Cys Leu Leu Tyr Val Phe Leu Tyr Leu Leu
100         105         110
Pro Ser Tyr Ile Leu Lys Ala Leu Phe Phe Leu Lys Gln Ile Leu Thr
115         120         125
Phe Leu Leu Ile Leu Asn Met Leu Leu Phe Ser Ala Trp Lys Thr Ile
130         135         140
Leu Lys Leu Thr His Pro Gln Lys Leu Phe Lys Asn His Leu Arg Ile
145         150         155         160
Gln Leu Lys Ser Glu Pro Ser Leu Glu Arg Leu Gly Lys Gly Thr Pro
165         170         175
Phe Asn Val Ser Thr Ile Ala
180

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<210> 133  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<400> 133

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Ile Glu Phe Val Leu Ser Arg Thr Pro His Ser Pro Thr Tyr Ile Tyr
1          5          10          15
Ala Pro Pro Met Cys Asn Ala Asn Glu Glu Asp Leu Ser Met Leu Leu
20          25          30
Thr Pro Lys Gly Glu Ile Ser Val Thr Asn Lys Leu Asp Asn Ala Phe
35          40          45
His Gly Asn Thr Leu Glu Phe Ser Ser Glu Phe Tyr Lys Trp Ile Leu
50          55          60
Phe Tyr Glu Val Thr Ser Phe Phe Ser Pro Cys Met Tyr Ala Ile Asp
65          70          75          80
Tyr Ser Lys Asn Val Tyr Ile Phe Leu Phe Ser Ser Phe Lys Ile Ser
85          90          95

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Val Glu Leu Gln Ser Val Tyr Leu Ile Ser Ser Val Ile Lys Asn Leu  
 100 105 110

Thr Lys Lys Leu Ile Ser Thr Ile Val Gly Lys  
 115 120

<210> 134  
 <211> 66  
 <212> PRT  
 <213> Homo sapiens

<400> 134

Gly Pro His Pro Thr Leu Trp Phe Ser Leu Leu Arg Gly Asn Gly Leu  
 1 5 10 15

Ala Pro Cys Arg Ser Leu Trp Glu Ala Asn Thr Phe Thr Arg Glu Pro  
 20 25 30

Trp Asn Pro Ala Pro Leu Arg Gly Pro Gly Arg Gln Trp Gly Leu Ala  
 35 40 45

Gly Leu Pro Val Leu Asn Ser Cys Ala Pro Asp Trp Val Pro Trp Ser  
 50 55 60

Tyr Ala  
 65

<210> 135  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens

<400> 135

Asn Ser Ile Phe Met Lys Asn Val Leu Thr Leu Val Val Leu Val Arg  
 1 5 10 15

Gly Ile Phe Phe Phe Gln Ala Tyr Ser Phe Pro Asn Asp Tyr Ser Phe  
 20 25 30

Cys Trp His Phe Ser Glu Gly Ile Leu Glu Ile Ser Leu Arg Val Arg  
 35 40 45

Lys Ala Thr Asn Cys Arg Gln Leu Pro Val Gly Leu Thr Phe Cys Arg  
 50 55 60

Ile His Ala Trp Cys Ala Glu Gly Gly Gln Gly Val Lys Asn Arg Lys  
 65 70 75 80

His Leu Met Cys Glu Phe Ile Ser Gly Ser Arg Arg Leu Pro Leu Arg  
 85 90 95

Trp Leu Met Leu Pro Ala Val Pro Pro Met Ser Ile Leu Gln Gly Leu  
 100 105 110

Ser Val Leu Trp Gly Tyr Glu Gln Ala Ser Glu Trp Gln Asp Tyr Leu  
 115 120 125

Glu Asn Leu Gly  
 130

<210> 136  
 <211> 189

<212> PRT  
 <213> Homo sapiens

<400> 136

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Ile Leu Val Gln Thr Ala Phe Val His Arg Lys Asn Leu Lys Glu Tyr
1          5          10          15
Asp His Leu Val Val Leu Leu Pro Val Lys Tyr Cys Cys Val Ile Phe
          20          25          30
Tyr Ser Ile Tyr Ile Ser Asn Thr Ser Met His Leu Val Ile Leu Cys
          35          40          45
Asp His Leu His Asn Asp Leu Phe Asn Thr Gln Gly Lys Cys Ile His
          50          55          60
Pro Tyr Val Ser Asp Glu Lys Ile Pro Asn Ser Phe His Cys Ser Glu
          65          70          75          80
Ala Phe Glu Thr Gln Ile Ser Cys Leu His Pro Ala Asn Asn Gln Lys
          85          90          95
Ile Ala Asn Cys Gln Tyr Cys Lys Asp Gln Thr Pro Lys Cys Pro Thr
          100          105          110
Arg Pro Cys Trp Pro Ala Pro Ser Ser Leu Ser Ser Leu Thr His Val
          115          120          125
Ser Leu Arg Glu Ala Ala Pro Leu Val Ser Tyr Gln Cys Leu Gln Ser
          130          135          140
Leu Ile Cys Leu Leu Ala Thr Gly Ser Leu His Val Leu Ser Tyr Ala
          145          150          155          160
Phe Phe Gly Leu Cys Leu Phe Leu Leu Asp Gln Glu Leu Thr Asn
          165          170          175
Phe Ser Leu Pro Ala Lys Phe Asn Tyr His Leu Phe Leu
          180          185

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<210> 137  
 <211> 200  
 <212> PRT  
 <213> Homo sapiens

<400> 137

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Leu Asn Ser Leu Arg Ala Cys Ser Asp Ser Leu Ala Tyr Ala Thr Ser
1          5          10          15
Gly Asn Arg Ser Phe Phe Lys Ile Thr Cys Ala Asp Leu Val Thr Gln
          20          25          30
Gly Asp His Thr Tyr Tyr Phe Leu Ser Ile Arg Asn Tyr Leu Trp Lys
          35          40          45
Gln Asp Asp Phe Ile Ser Cys Leu Ala Leu Pro Leu Leu Phe Thr Glu
          50          55          60
Asn Gln Gln His Ala Asn Asp Val Leu Lys Val Gln Ser His Leu Arg
          65          70          75          80
Thr Leu Gly Ser Leu Ala Arg Glu Thr Leu Tyr Asp Thr Val Phe Lys
          85          90          95

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Cys Thr Pro Ile Gln Asn Cys Lys Tyr Leu Phe Cys Thr Asp Leu Ala  
 100 105 110  
 Cys Thr Lys Gln Pro Tyr Thr Val Tyr Ile Lys Cys Thr Ser Arg Leu  
 115 120 125  
 Ser Ile Arg Lys Arg Gly Lys His Pro Asn Tyr Ile Gln Arg His Tyr  
 130 135 140  
 Trp Lys Leu Ile Met Tyr Asn Ser Gln Tyr Asn Ala Asn Ile Tyr Pro  
 145 150 155 160  
 Arg Val Ile Gln Phe Leu Thr Val Gly Glu Ile Ala Phe Ile Pro Asn  
 165 170 175  
 Leu Thr Leu Leu Arg Leu Lys Gln Lys Val Met Leu Val Cys Ile Phe  
 180 185 190  
 Pro Gln Ile Leu Asn Arg Tyr Phe  
 195 200

<210> 138  
 <211> 215  
 <212> PRT  
 <213> Homo sapiens

<400> 138

Gly Lys Glu Lys Ser Asp Tyr Phe Ser Thr Thr Ala Ile Phe Lys Leu  
 1 5 10 15  
 Leu Glu Ala Val Cys Ile Pro Ser Ser Glu Val Ser Gly Ser Ser Pro  
 20 25 30  
 Cys Val Ala Glu Arg Arg Leu His Pro Ser Ser Leu Pro Lys Ala Thr  
 35 40 45  
 Thr Ala Tyr Leu Arg Ile Thr Thr Ile Ser Cys Asp Pro Tyr Ile Ala  
 50 55 60  
 Met Val Asn Leu Ser Ile Asp Leu Tyr Tyr Ile Met Gly Leu Gln Gln  
 65 70 75 80  
 Phe Cys Lys Leu Asp Glu Asp Phe Tyr Lys Glu Tyr Trp Arg Leu Gly  
 85 90 95  
 Glu Val Thr Cys Asp Gly His Ile Pro Gly Ser Met Tyr Thr Ile Ser  
 100 105 110  
 Leu Leu Gly Leu Cys His Thr Val Leu Ser Cys Ser Trp Gly Asn Ile  
 115 120 125  
 Ser Gly Thr Cys Leu Ile Arg Val Val Cys Cys Gly Gln Gln Arg Asp  
 130 135 140  
 Gly Cys Val Ser Gly His Leu Pro His Thr Gln Val Pro Leu Arg Thr  
 145 150 155 160  
 Leu Ala Leu Thr Leu Lys Asn Gln Leu Val Val Cys Leu Gln Arg Asn  
 165 170 175  
 Cys Phe Gln Gly Pro Phe Ser Ala Leu Thr Phe His Gln Val Ser Pro  
 180 185 190



Leu Ala Pro Ala Gln Ser Ser Lys Ile Phe Leu Thr Thr Pro Val Ser  
 195 200 205

Asp Val His Gln Met Leu Ile  
 210 215

<210> 139  
 <211> 163  
 <212> PRT  
 <213> Homo sapiens

<400> 139

Gly Trp Lys Asp His Ser Asp Thr Val Ala Gly Ala Cys Trp Glu Gln  
 1 5 10 15

Glu Trp Lys Gln Gly Trp Asp Phe Ser Leu Gln Pro Thr Ile Met Val  
 20 25 30

Leu Thr Ser Leu Val Leu Ala Gly Leu Thr Cys Phe Ser Ala Arg Gly  
 35 40 45

Ala Leu Gly Asn Gln Ser Ala Glu Asp Thr Cys Ser Ser Val Phe Thr  
 50 55 60

Pro Tyr Trp Gln Leu Ser Trp Cys Asn Ala Leu Asp Trp Ala Leu Gly  
 65 70 75 80

Arg Leu Asn Gln Ser Ser Pro Arg Thr Gly Asn Phe Leu Gly Ala Met  
 85 90 95

Pro Leu Thr Gly His Trp Glu Gly Cys Lys Asn Ser Phe Cys Pro Gln  
 100 105 110

Glu Glu Gln Arg Val Gly Leu His Pro Asp Asn Cys Pro Thr Asn Gly  
 115 120 125

Met Cys Arg Pro Gly Gly Ala Gly Ala Val Ala Leu Met Leu Phe Pro  
 130 135 140

Val Leu Leu Glu Gly Gly Ser Met Pro Trp Arg Gln Leu His Gly Ser  
 145 150 155 160

Trp Gly Ser

<210> 140  
 <211> 194  
 <212> PRT  
 <213> Homo sapiens

<400> 140

Ile Met Ile Asp Arg Asp Val Gln Pro Phe Gly Asp Leu Arg Ala Gln  
 1 5 10 15

Pro Gly Glu Gln Gly Val Ser Glu Val Leu Leu Ser Thr Ala Ile Leu  
 20 25 30

Asn Ser Pro Asn Leu Gln Pro Gly Pro Leu Ser Phe His Glu Leu Thr  
 35 40 45

Ser Gln Pro Leu Phe Cys Cys Leu Trp Arg Lys Asn Asp Val Val Lys  
 50 55 60

Thr Phe Glu Asn Gln Asp Leu Asn Asn Lys Phe Ile Ala Arg Cys Phe  
 65 70 75 80  
 Pro Ile Gly Lys Lys Glu Tyr Met Asn Glu Ile Gln Leu Ser Thr Ser  
 85 90 95  
 Ala Asn Ser Thr Asp Ser Glu Phe Lys Gly Pro Phe Pro Ala Leu Ser  
 100 105 110  
 Leu Met Thr Leu Thr Gly Cys Phe Ser Leu Ser Trp Leu His Leu Met  
 115 120 125  
 Gly Ala Ser Trp His Leu Leu Cys Gly Gln Gly Val Glu Lys Thr Pro  
 130 135 140  
 Pro Ala Val Asn Ser Leu Thr Val Asn Ile Cys Val Asn Ile Cys Leu  
 145 150 155 160  
 Glu Asp Leu Ser His Thr Pro Thr Ile Leu Thr Asn Ile Lys Gly His  
 165 170 175  
 Gly Asp Glu Ser Leu Asn Ser Ala Pro Ser Leu Pro Leu Gln Gly Gln  
 180 185 190

Met Cys

<210> 141  
 <211> 320  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 141

Tyr Leu Phe Leu His Ser Gln Arg Ser His Gln Lys Gln Pro Val Leu  
 1 5 10 15  
 Cys Ser Gln Ser Gln Thr Asn Ala Lys Ala Leu Lys His Lys Arg Ser  
 20 25 30  
 Gln Glu Val Ser Ala Asn Leu Asp Leu Lys Thr Asn His Ile Val Ile  
 35 40 45  
 Gly Trp Gly Lys Val Ile Ile Pro His Arg Ser Tyr Val Pro Thr Gly  
 50 55 60  
 Thr Ile Thr Glu Asn Lys His His Arg Gly Trp Met Thr Phe Glu Ser  
 65 70 75 80  
 His Asn Ala Lys Leu Glu Leu Gly Leu Lys Pro Lys Phe Leu Ala His  
 85 90 95  
 Arg Ser Ser Asp Pro Pro Ile Pro His Ala Ile Pro Gly Ser Leu Leu  
 100 105 110  
 Leu Gly Phe Phe Ser Ala Glu Glu Arg Asn Ser Gly Phe Gln Lys Leu  
 115 120 125  
 Leu Ala Thr Leu Pro Phe Thr Val Tyr Ser Gln Trp Glu Glu Gly Leu  
 130 135 140  
 Leu His Ser Ser Leu Leu Ser Pro Glu Arg Arg Leu Pro Gln Ala Cys  
 145 150 155 160  
 Ile Trp Gly Lys Gln Ala Gly Ser Ala Val Val Lys Ser Thr Ala Pro

165                      170                      175  
 Gln Gln Ser Glu Arg Ser Val Ser Asn Leu Gln Ala Met Gln Pro Lys  
       180                      185                      190  
 Ser Gln Tyr Pro Ser Leu Tyr His Glu Asp Asn Thr Gly Thr Asn Phe  
       195                      200                      205  
 Leu Gly Val Leu Ala Phe Asn Gly Cys His Met Arg Cys Leu Ala Pro  
       210                      215                      220  
 Ser Lys Pro Thr Asp Ala Asp His Phe Thr Val His Arg Lys Leu Ser  
       225                      230                      235                      240  
 Lys Ile His Pro Ala Leu Ser Gly Asn Val Leu Val Ile Ser Leu Ser  
                              245                      250                      255  
 Thr His Ile Ile Thr Lys Ser Glu Ser Lys Tyr Ser Arg Ala Leu Asn  
                              260                      265                      270  
 Pro Thr Thr Leu Met Ser Leu Leu Arg Gly Gly Arg Asp Val Ala Phe  
                              275                      280                      285  
 Leu His Cys Asn Ser Gln Phe Gln Tyr Ser Ile Phe Phe Phe Arg Asn  
                              290                      295                      300  
 Phe Cys Ile Gln Leu Thr Val Leu Val Arg Arg Ala Glu Gly Glu Gly  
       305                      310                      315                      320

<210> 142  
 <211> 310  
 <212> PRT  
 <213> Homo sapiens

<400> 142

Lys Leu Ser Asn Thr Gln Lys Lys Ser Arg Ile Ile Glu His Arg Leu  
       1                      5                      10                      15  
 Ile Ala Thr Ile Leu Ser Arg Ile Ile Ala Val Cys Asp Asn Phe Phe  
                              20                      25                      30  
 Val Ser Ile Phe Asp Cys Ile Phe Ser Met Thr Lys Ser Asn Ser Arg  
                              35                      40                      45  
 Glu Gly Gln Ser Trp Phe Tyr Ser Pro Phe Tyr Arg Gln Asn Leu Ala  
                              50                      55                      60  
 Gln Cys Leu Leu Tyr Thr Met Phe Gln Leu Tyr Ile Cys Met Asn Phe  
       65                      70                      75                      80  
 Ile Ile Ile Pro Lys Met His Val Leu Ala Val Gln Tyr Tyr Lys Lys  
                              85                      90                      95  
 Ile Leu Val Val His Leu Lys Gly Asn His Phe Phe Leu Leu Gln Ala  
                              100                      105                      110  
 Ile Ile Thr Asn Leu Phe Arg Ala Leu Gln Met Ile Lys Ala Leu Tyr  
                              115                      120                      125  
 Leu Ser Ile Ile Ile Arg Ile Thr Leu Leu Phe Ile Gln Leu Ser Ser  
                              130                      135                      140  
 Ile Pro Ser Ser Val Ser Phe Arg Lys Ser Phe Gly Gly Glu Phe Asn  
       145                      150                      155                      160

Thr Val Gly Arg Lys Leu Leu Gly Met Tyr Asn Ile Ser Phe Ser Val  
 165 170 175  
 Ile Lys Tyr Asn Phe Cys Trp Asn Ala Phe Ala Ser Ser Leu Val Lys  
 180 185 190  
 Ile Leu Phe Asn Ser Pro Ile Cys Ser Asp Phe Asp Met Leu Thr Trp  
 195 200 205  
 Leu Gly Tyr Ser Pro Gln Leu Leu Asn Gln Met Ile Ile Gln Leu Phe  
 210 215 220  
 Leu Pro Phe Ala Asp Val Ile Gln Ser Thr Thr Ser Ile Trp Val Lys  
 225 230 235 240  
 Lys Phe Arg Ile Tyr Val Cys Ile Leu Trp Val Gly Leu Ile Gln Ser  
 245 250 255  
 Val Gly Arg Leu Lys Lys Gln Gly Ser Leu Ser Gln Lys Glu Lys Ile  
 260 265 270  
 Val Cys Leu Trp Ile Lys Ala Leu Ala His Thr Cys Val Ser Ala Ser  
 275 280 285  
 Gln Ile Ser Asp Cys Leu Ala Ser Pro His Ile His Val Ser Gln Phe  
 290 295 300  
 Leu Lys Ile Asn Leu Leu  
 305 310

<210> 143  
 <211> 316  
 <212> PRT  
 <213> Homo sapiens

<400> 143

Leu Gly Ile Cys Ser Phe His Phe Ser Tyr Cys Leu Thr Ser Leu Leu  
 1 5 10 15  
 Tyr Phe Leu Leu Ser Phe Phe Thr Phe Gln Ser Ser Leu Ile His Ser  
 20 25 30  
 Leu Ala Gly Phe Asn Leu Ala Leu Pro Tyr Ser Leu Ser Phe Leu Asn  
 35 40 45  
 Lys Tyr Leu Asn Phe Tyr Val Thr Phe Lys His Phe Leu Cys Asn Leu  
 50 55 60  
 Leu Leu Thr His Thr Glu Ile Leu Leu Lys Val Leu Ser Cys Tyr Ile  
 65 70 75 80  
 Leu Lys Val Ser Val Cys Ser Leu Phe Phe Pro Arg Asp Asn Cys Phe  
 85 90 95  
 Phe Thr Phe Tyr Ile Ser Phe Phe Leu Cys Phe Gln Phe Phe Gln Leu  
 100 105 110  
 Tyr Tyr Lys Lys Phe Gln Thr Glu Asn Leu Asn Lys Trp Tyr Asn His  
 115 120 125  
 Arg Asn Phe Leu Arg Phe Asp Tyr Leu Phe Val Phe Ala Phe Leu Phe  
 130 135 140

Leu Cys Met Leu Ile Ser Ile Thr Pro Phe Glu Val Lys Phe Pro Ser  
 145 150 155 160  
 Asn Gln Arg Lys Asn Ser Gly Tyr Phe Ile Gly Arg Gly Thr Gly Glu  
 165 170 175  
 Pro Ser Lys Ala Ser Gly Asn Val Leu His Leu Asn Leu His Gly Ser  
 180 185 190  
 Tyr Thr Cys Lys Asn Ser Glu Arg Tyr Thr Ser Asp Leu Tyr Pro Leu  
 195 200 205  
 Leu Cys Ile Ser Ser Ile Ser Lys Lys Arg Gly Phe Ala Gly Glu Val  
 210 215 220  
 Ala Val Ile Leu Thr Leu Tyr Ser Ile Leu Ile His Val Ile Pro Lys  
 225 230 235 240  
 Asn Lys Asp Ile Leu Leu Tyr Asn Tyr Val Thr Ile Leu Thr Phe Lys  
 245 250 255  
 Asn Val Asn Ser Ile Thr Ile Cys Ser Ile Gln Ser Met Leu Lys Ile  
 260 265 270  
 Ser Gln Val Pro Arg Met Ile Leu Pro Pro Ser Gly Leu His Thr Ala  
 275 280 285  
 Phe Gly Cys Tyr Val His Leu Val Leu Tyr Ser Val Glu Ser Pro Thr  
 290 295 300  
 Phe Leu Leu Ser Lys Thr Leu Thr Tyr Gln Gly Val  
 305 310 315

<210> 144  
 <211> 204  
 <212> PRT  
 <213> Homo sapiens

<400> 144

Glu Ile Ile Arg Val Tyr Pro Leu Thr Ser Ser Pro Ser Gly Asn Ile  
 1 5 10 15  
 Leu Gln Asn Asn Gly Thr Gly Ser Pro Gly Tyr His Gln Ser Gln Gly  
 20 25 30  
 Ser Tyr Arg Thr Ala Leu Leu Pro Gln Gly Ser Leu Cys Trp Leu Phe  
 35 40 45  
 Ile Thr Thr Val Arg Met Leu Leu Pro Leu Leu Asn Tyr Gln Gln Pro  
 50 55 60  
 Leu Ile Cys Ser Ser Phe Leu Gln Cys His Phe Asn Ser Val Val Met  
 65 70 75 80  
 Glu Ser Met Leu Tyr Ile Thr Phe Trp Asp Trp Leu Phe Ser Leu Cys  
 85 90 95  
 Ile Ile Pro Ser Arg Ser Ile Lys Trp Leu Ser Met Val Val His Ser  
 100 105 110  
 Val Ser Leu Val Ser Lys Ser Asp Leu Phe Gln Val Asn Ile Gly Ser  
 115 120 125  
 His Cys Ser Thr Ala Ser Leu Ser Ser Ser Pro Trp Asn Asp Ser Gln

130 135 140  
 Ala Pro Cys Thr Gly Thr Leu Thr Pro Ala Trp Leu Ser Ser Leu His  
 145 150 155 160  
 Ala Ile Arg Ser Leu Leu Val Cys Phe Ala Pro Val Thr Trp Val Ser  
 165 170 175  
 Cys Gln Tyr Ile Asn Ser Gln Cys Phe Ser Ala Tyr Pro Ser Ser Pro  
 180 185 190  
 Thr Leu Val Phe Asp Phe Thr Val Ser Ser Ala Trp  
 195 200

<210> 145  
 <211> 99  
 <212> PRT  
 <213> Homo sapiens

<400> 145

Phe Leu Phe Glu Lys Ser His Cys Thr Glu Tyr Ile Asn Glu Phe Ser  
 1 5 10 15  
 Glu Asp Ile Cys Val Lys Ser Gly Leu Ser Gly Thr Val Cys Leu Lys  
 20 25 30  
 Leu Trp Lys Glu Ile Leu Phe Phe Phe Ser Ala Phe Val Ser Ser Asn  
 35 40 45  
 Phe Leu Ile Val Ile Ser Gln Gly Pro His Arg Cys Ile Trp Ala Thr  
 50 55 60  
 Gly Phe Phe Cys Phe Phe Phe Phe Thr Cys Cys Leu Ser Ile Pro Asn  
 65 70 75 80  
 Arg Gly His Gln Ile Pro Gly His Leu Val Val Leu Val His Gly Leu  
 85 90 95  
 Leu Gly Thr

<210> 146  
 <211> 57  
 <212> PRT  
 <213> Homo sapiens

<400> 146

Thr Val Phe Asn Glu Glu Phe Trp Gln Ala Phe Pro Pro Ile Val Pro  
 1 5 10 15  
 Phe Arg Lys Ala Ser Ser Tyr Ser Val Met Thr His Val Ile Phe Cys  
 20 25 30  
 Val Leu Pro His Arg Asp Cys Leu Phe Phe Phe Leu Phe Ser Glu Thr  
 35 40 45  
 Trp Ile Asn Ser Trp Tyr Leu Glu Ser  
 50 55

<210> 147  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 147

Val Cys Phe Val Ile Ile Ser Phe Phe Leu Trp Val Leu Pro Leu Val  
 1 5 10 15  
 Val Leu Val Cys Leu Pro Gly Lys Phe Leu Thr Leu Ala Phe Asp Leu  
 20 25 30  
 Leu Leu Leu Leu Ser Ile Val Val Ser Met Pro His Leu Val Ile Tyr  
 35 40 45  
 Phe Leu Ala Glu Leu Tyr Arg Lys Arg His Arg Glu Ser Leu Lys Ala  
 50 55 60  
 Val Phe Gln Arg Ala Leu Leu Ser Glu Met Glu Ala Trp Ile Lys Gly  
 65 70 75 80  
 Val Ser Gly Pro Arg Ser Gln Gly Arg Phe Gln Pro His Ser Trp Lys  
 85 90 95  
 Gln Thr Ala Leu Leu Gly Gly Ser Ala Pro Pro Gln Arg Gln Gly Leu  
 100 105 110  
 Pro Met His Lys Ala Val Lys Gly Ile Met Ser Gly Lys His Ala Glu  
 115 120 125  
 Ser Ser Lys Glu Gln Gly Glu Cys Ser Asp Tyr Leu Leu Pro Leu Cys  
 130 135 140  
 Ile Phe Arg Val Thr Arg Phe Leu Thr Glu Phe Lys Thr Lys Leu Leu  
 145 150 155 160  
 Cys Phe Cys Pro Ile Ile Leu Asn Ser His Gly Asn Pro Leu Glu Arg  
 165 170 175  
 Gln Val Arg Ser Lys Ala Asp Leu Pro Gly Phe Phe Phe Phe Phe Phe  
 180 185 190

&lt;210&gt; 148

&lt;211&gt; 122

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 148

Ile Gly Phe Ser Leu Pro Leu Leu Leu Leu Lys Ile Val Leu Ile Gly  
 1 5 10 15  
 His Phe Leu Leu Lys Pro Arg Pro Leu Trp Lys Cys Gly Ala Tyr Arg  
 20 25 30  
 Glu Val Arg Arg Pro Arg Ser Ala Ala Arg Thr Arg Arg Pro Leu Thr  
 35 40 45  
 Arg Val Cys Ala Ser Cys Glu Lys Ala Phe Leu Ala Ser Leu Asn Ala  
 50 55 60  
 Cys Phe Thr Cys Ser Leu Phe Leu Ile Ser Phe Pro Asn Cys Val Pro  
 65 70 75 80  
 Ser Ile Leu Leu Tyr Cys Ser Leu Cys Trp Glu Gly Arg Tyr Glu Asn  
 85 90 95  
 Val Ala Tyr Ile Lys Thr Ala Glu Ser Cys Ile Leu Cys Cys Pro Glu

100 105 110  
 Ser Arg Asn Thr Val Leu Leu Leu Ala Val  
 115 120  
 <210> 149  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens  
 <400> 149  
 Leu Ser Pro Asp Thr Ile Arg Met Asn Ala Asp Cys Cys Ile Ser Gly  
 1 5 10 15  
 Met Trp Leu Thr Ala Ala Ala Thr Cys Leu Gln Glu Cys Pro Cys Leu  
 20 25 30  
 Val Ser Val Thr Arg Cys Ser Val His Leu Asp Gln Tyr Ile Thr Phe  
 35 40 45  
 Thr Asn Val Ser Glu Arg Asn Val Arg Ile Asn Gln Asp Ile Ser Leu  
 50 55 60  
 Leu Val Phe Phe Phe Trp Gln Ala Ala Leu Thr Ile Val Leu Glu Pro  
 65 70 75 80  
 Thr Pro Tyr Val Asn Ile Ile Gln Ser Ser Ile Ser Lys Ala Gly Ser  
 85 90 95  
 Gln Glu Met Leu Phe Ile Arg Arg His Ile Gly Tyr Ser Leu Gln Asn  
 100 105 110

Val Lys

<210> 150  
 <211> 235  
 <212> PRT  
 <213> Homo sapiens  
 <400> 150  
 Met Val Pro Met Ser Pro Leu Arg Cys Arg Leu Asn Pro His Thr Thr  
 1 5 10 15  
 Leu Gly Val Val Val His Ala Phe Pro Tyr Ser Ser Gly Asp Gln Asn  
 20 25 30  
 Cys Ile Gly Pro Val Arg Arg Gly Thr Trp Ile Leu Glu Ser Asn Lys  
 35 40 45  
 Pro Phe Ser His Phe Leu Val Gly Pro Ala Ser Lys Leu Thr Phe Leu  
 50 55 60  
 Ser Leu Ser Ser Ser Ile Lys Trp Glu Lys Leu His Leu Leu His Gly  
 65 70 75 80  
 Thr Ala Ile Arg Phe Lys Ile Met Val Ile Asn Asn Leu Val Gln Tyr  
 85 90 95  
 Leu Val Tyr Thr Lys Cys Ser Ile Asn Ala Thr Ala Ile Cys Ser Ser  
 100 105 110  
 His Pro Ile Leu Phe Phe Val Asp Asn Arg Phe Asn Ser Leu Ser Ile



115                      120                      125  
 Lys Pro Gly Lys Lys Arg Asp Glu His Arg Pro Trp Ser Arg Ser Ile  
     130                      135                      140  
 Lys Asp Ser Lys Gly Phe Ser Ser Gly His Pro Phe Pro Met Cys Trp  
     145                      150                      155                      160  
 Pro Asn His Val Pro Leu Trp Ser Ser Arg Leu Tyr Gly Leu Phe Asn  
                     165                      170                      175  
 Ser Thr Lys Ala Gln Val Asn Ile Pro Thr Pro Ser Asn Met Ser Thr  
                     180                      185                      190  
 Gly Pro Val Gly Asn Ser Val Ala Gly Gln Ala Leu Cys Ser Val Ser  
                     195                      200                      205  
 Ala His Gly Leu Ser Thr His Pro Asp Gln Pro Pro Val Leu Thr Ala  
                     210                      215                      220  
 Phe Leu His Gln Ile Leu Thr Ser Asn His Pro  
     225                      230                      235  
  
 <210> 151  
 <211> 202  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 151  
  
 Met Leu Gly Gly Pro Gly His Gly Gly Leu Ala His Arg Gly Ser His  
     1                      5                      10                      15  
 Trp Glu Ile Gly Asn Leu Phe Phe Ala Gly Pro Asp Gln Tyr Ile Pro  
                     20                      25                      30  
 Leu Val Leu Gly Glu Pro Ser Gln Pro Pro Asn Ser Ser Trp Pro Leu  
                     35                      40                      45  
 Ser Gln Asn Gly Thr Asn Thr Glu Ala Thr Pro Ala Thr Asn Leu Thr  
                     50                      55                      60  
 Phe Ser Ser Tyr Tyr Gln His Thr Ser Pro Val Ala Ala Met Phe Ile  
     65                      70                      75                      80  
 Val Ala Tyr Ala Leu Ile Phe Leu Leu Cys Met Val Gly Asn Thr Leu  
                     85                      90                      95  
 Val Cys Phe Ile Val Leu Lys Asn Arg His Met His Thr Val Thr Asn  
                     100                      105                      110  
 Met Phe Ile Leu Asn Leu Ala Val Ser Asp Leu Leu Val Gly Ile Phe  
                     115                      120                      125  
 Cys Met Pro Thr Asn Pro Leu Asp Asn Leu Ile Thr Gly Glu Cys Gly  
                     130                      135                      140  
 Gln Leu Ala Ala Gly Val Ser Pro Thr Pro His Phe Asn Phe Ser Asp  
     145                      150                      155                      160  
 Lys Ala Gly Asn Gln Ser Leu Glu Asp Arg Tyr His Cys Trp Ala Gly  
                     165                      170                      175  
 Leu Leu Ala Met Pro Trp Tyr Ser Asn Ser Ser Arg Gln Ser Trp Gly  
                     180                      185                      190

Arg Val Arg Leu Val Asn Lys Arg Phe Asn  
195 200

<210> 152  
<211> 176  
<212> PRT  
<213> Homo sapiens

<400> 152

Met Leu His Leu Lys Val Thr Lys Leu Cys Val His Ile His Ile Ala  
1 5 10 15  
Asn Pro Pro Lys Leu Met Ser Leu Leu Trp Phe Gly Tyr Gly Leu Phe  
20 25 30  
Ile Pro Thr Lys Ile His Ile Glu Ile Ser Ser Pro Val Cys Trp Glu  
35 40 45  
Val Gly Pro Ser Trp Gly Met Ala Trp Cys His Ser Leu Gly Ser Gly  
50 55 60  
Val Leu Ala Val Ala Arg Met Asn Phe Leu Arg Glu Ile Leu Asn Ser  
65 70 75 80  
Ser Cys Gln Ser Glu Phe Leu Ser Gln Asp Ala Pro Trp Val Leu Ser  
85 90 95  
Leu Phe Thr Cys Pro Leu Ser Leu Pro Ser Leu Leu Cys Phe Asp Leu  
100 105 110  
Ala Asp Leu His Gln Lys Pro Ser Arg Cys Gln His Arg Ala Ser Leu  
115 120 125  
Thr Phe His Leu Gln Asn Cys Glu Leu Asn Lys Pro Leu Phe Phe Ile  
130 135 140  
Asn Tyr Leu Ala Ser Val Phe Cys Tyr Ser Asn Thr Lys Trp Thr Lys  
145 150 155 160  
Thr Val Ser Gln Thr Asn Cys Gly Leu Phe Leu Lys Val Thr Pro Thr  
165 170 175

<210> 153  
<211> 252  
<212> PRT  
<213> Homo sapiens

<400> 153

Leu Asn Thr Glu Cys Gln His Glu Pro Glu Val Met Leu Val His Gly  
1 5 10 15  
Arg Phe Leu Ser Asn Val Ile Leu Ser His Gln Val Thr Ala Ala Met  
20 25 30  
Ser Lys Ile His Lys Tyr Ser Ala Cys Lys Pro Lys Arg Pro Val Val  
35 40 45  
Leu His Pro Thr Cys Phe Leu Phe Val Trp Phe Gly Tyr Met Phe Cys  
50 55 60  
Leu Gly Ile Asn Cys Leu Leu Tyr Asn Leu Pro Gly Ser Leu Ser Ile  
65 70 75 80

Leu Pro Leu His Pro Lys Leu Gly Ser Leu Asn Pro Tyr Ile Lys Phe  
                     85                    90                    95  
 Ile Ser Pro Val Asn Ser Ala Ser Ile Leu Ile Phe Thr Ala Phe Leu  
                     100                    105                    110  
 Ser Ala Ala Leu Ile Lys Phe Asn Ile Phe Glu Val Asp Tyr Pro Leu  
                     115                    120                    125  
 Pro Tyr Phe Pro Pro Thr Thr Lys Ala Leu Gln Leu Leu Leu Tyr Ser  
                     130                    135                    140  
 Ala Glu His Arg Trp Glu His Arg Cys His Ile Thr Ala Glu Ile Ser  
                     145                    150                    155                    160  
 Ile Leu Val Arg Thr His Pro Asp Ser Asp Met Lys His Ile Val His  
                     165                    170                    175  
 Thr Thr Ile Ala His Arg Phe His Gln Glu Met Ser Ala Asp Ser Asp  
                     180                    185                    190  
 Glu Gly Pro Thr Thr Pro Ser Gly Trp Arg Val Leu Asp Ser Ser Leu  
                     195                    200                    205  
 Ser Pro Leu Pro Thr Pro Phe His Val Pro Ala Ser Gln His Glu Ala  
                     210                    215                    220  
 Ala Ser Gln Gln Cys Gln Arg Thr Thr Asp Arg Pro Arg Thr Asn His  
                     225                    230                    235                    240  
 Ile His Pro Trp Lys Arg Ser Ser Val Tyr Tyr Met  
                     245                    250

<210> 154  
 <211> 205  
 <212> PRT  
 <213> Homo sapiens

<400> 154

Lys Leu Ser Pro Trp Gly Ser Ser Leu Trp Asn Val Asn Ile Ser His  
 1                    5                    10                    15  
 Leu Ile Val His Phe Leu Lys Ser Lys Tyr Met Asp Lys Val Tyr Ala  
                     20                    25                    30  
 Phe Pro Thr Glu Val Tyr Arg Gly Val Ile Lys Phe Ala Tyr Lys Ile  
                     35                    40                    45  
 Phe Leu Asn Tyr Asp Leu Gly Arg Asp Val Val Val Ile Glu Ile Ile  
                     50                    55                    60  
 Phe Trp Asn Cys Lys Ser Asn Met Tyr Asn Tyr Leu Ala Val Leu Pro  
                     65                    70                    75                    80  
 Ala Leu Ser Leu Thr Leu Pro Ile Ser Gly Ser Phe Leu Leu Ile Gly  
                     85                    90                    95  
 Phe Gln Asp Lys Lys Cys Phe Leu Arg Asp Gly Phe Cys Val His Leu  
                     100                    105                    110  
 Phe Lys Arg Ser Pro Leu Ser Ser Cys His Leu Leu Thr Asn Tyr His  
                     115                    120                    125

Val Tyr Ser Leu Leu Trp Phe Gly Tyr Gly Leu Leu Val Pro Thr Lys  
 130 135 140  
 Ser Tyr Val Glu Ile Met Ile Ser Arg Val Val Val Leu Gly Gly Gly  
 145 150 155 160  
 Ala Glu Val Leu Ala Ser Trp Gly Gln Ile Pro Cys Lys Trp Leu Gly  
 165 170 175  
 Ala Ile Leu Met Gly Val Asn Glu Phe Leu Leu Phe Asp Trp Val Ala  
 180 185 190  
 Ser Gly Lys Gly Ile Ser Leu Pro Pro Ser Gly Leu Val  
 195 200 205

<210> 155  
 <211> 113  
 <212> PRT  
 <213> Homo sapiens

<400> 155

Val Ser Gly His Phe Phe Trp Ser Cys Gly Phe Lys Val Ser Thr Thr  
 1 5 10 15  
 Leu Leu Ile Val Asp Lys Asn Gly Ser Met Trp Val Tyr Ile Leu Ile  
 20 25 30  
 Trp Ser Cys Ser Tyr Ser Lys Ala Val Glu Ala Arg Ser His Ser Phe  
 35 40 45  
 His Asp Ile Leu Met Ser Ser Leu Gly Arg Val Val Gly Val Val Ile  
 50 55 60  
 Val Ser Gly Asp Lys Trp Gln Arg Leu Thr Gln Tyr Ser Phe Cys Leu  
 65 70 75 80  
 Thr Ala Glu Phe Lys Pro Phe His Leu Leu Leu Val Leu Ser Thr Arg  
 85 90 95  
 Gly Arg Lys Tyr Lys Leu Asp Cys Ala Leu His Arg Leu Tyr Ile Ile  
 100 105 110

Ile

<210> 156  
 <211> 181  
 <212> PRT  
 <213> Homo sapiens

<400> 156

Leu Leu Tyr Leu Ser Leu Tyr Ile Tyr Gln Asp Leu Ser Arg Pro Pro  
 1 5 10 15  
 Gly Tyr Pro His Phe Val Asn Asp Pro Val Trp Ser Ser Ile Cys Gln  
 20 25 30  
 Ala Val Gly Asn Arg Ala Leu Val Ser Val Phe Ser Phe Cys Asp Ala  
 35 40 45  
 Gly Ser Pro Val Leu Thr Gln Asp Leu Leu Met Gly Arg Thr Tyr Val  
 50 55 60

Pro Ser Arg Glu Ala Cys Gly Arg Glu Phe Leu Pro Ser Arg His Leu  
 65 70 75 80  
 Leu Trp Phe Gly Tyr Gly Leu Cys Gly Pro Thr Lys Phe His Val Gly  
 85 90 95  
 Ile Cys Pro Pro Ser Ile Gly Gly Thr Ala Trp Trp Glu Leu Phe Gly  
 100 105 110  
 Leu Trp Glu Trp Ile Val Tyr Glu Cys Leu Gly Ala Ile Leu Met Arg  
 115 120 125  
 Val Asn Ser Cys Lys Asn Trp Leu Leu Lys Arg Ala Trp His His Leu  
 130 135 140  
 Leu Ser Leu Leu Ala Phe Leu Ser Tyr His Val Leu Ser Val Tyr Ala  
 145 150 155 160  
 Ser Ser Leu His Leu Pro Pro Arg Val Glu Ala Ser Gly Phe Ile Arg  
 165 170 175  
 His Arg Tyr Trp Cys  
 180

<210> 157  
 <211> 190  
 <212> PRT  
 <213> Homo sapiens

<400> 157

Lys Lys Leu Val Arg Asp Cys Val Gly Asp Leu Cys Met Ala Gln Lys  
 1 5 10 15  
 Cys Pro Leu Ser Ile Leu Tyr Lys Leu Lys Thr Thr Asn Leu Asn Phe  
 20 25 30  
 Val Leu Cys Ser His Gln Ser Leu Thr Val Ser Pro Leu Phe Ala Ser  
 35 40 45  
 Tyr Val Lys Gly Thr Ile Phe Phe Glu Arg Cys Gln Asp Phe Ser Met  
 50 55 60  
 Leu Cys Phe Thr Leu Phe Trp Phe Cys Met Leu His Phe Arg Gln Arg  
 65 70 75 80  
 Ala Ala Val Lys Ser Tyr Arg Lys Ala Val Lys Thr Pro Trp Asn Tyr  
 85 90 95  
 Phe Tyr Phe His Phe Ile Leu Ala Asp Pro Ala Tyr Ile Tyr Leu Phe  
 100 105 110  
 Ile Thr Cys Leu Asn Val Glu Ser Phe Trp Val Ala Leu Ala Leu Asn  
 115 120 125  
 Glu His Leu Glu Arg Ala Leu Ile Pro Ala Trp Ile Ile Ala Leu Leu  
 130 135 140  
 Leu Pro Arg Ile Leu Thr His Phe Pro His Leu Arg Glu Val Leu Lys  
 145 150 155 160  
 Phe Leu Arg Pro Arg Phe Val Ser Glu Cys Val Ile Met Gly Thr Asn  
 165 170 175  
 Glu Ile Met Phe Ile Arg Gly Phe Val Phe Phe Ile Val Val

180 185 190

<210> 158  
 <211> 221  
 <212> PRT  
 <213> Homo sapiens

<400> 158

Ala Ser Leu Ala Cys Asn Ala Ser Leu Leu Pro Ser Leu Pro Tyr Phe  
 1 5 10 15  
 Glu Thr Phe Asn Cys Leu Leu Ala Leu Tyr His Thr Phe Ser Tyr Ile  
 20 25 30  
 Thr Phe Phe Ile Gly Leu Ser Leu Leu Tyr Leu Ser Leu Tyr Ile Tyr  
 35 40 45  
 Gln Asp Leu Ser Arg Pro Pro Gly Tyr Pro His Phe Val Asn Asp Pro  
 50 55 60  
 Val Trp Ser Ser Ile Cys Gln Ala Val Gly Asn Arg Ala Leu Val Ser  
 65 70 75 80  
 Val Phe Ser Phe Cys Asp Ala Gly Ser Pro Val Leu Thr Gln Asp Leu  
 85 90 95  
 Leu Met Gly Arg Thr Tyr Val Pro Ser Arg Glu Ala Cys Gly Arg Glu  
 100 105 110  
 Phe Leu Pro Ser Arg His Leu Leu Trp Phe Gly Tyr Gly Leu Cys Gly  
 115 120 125  
 Pro Thr Lys Phe His Val Gly Ile Cys Pro Pro Ser Ile Gly Gly Thr  
 130 135 140  
 Ala Trp Trp Glu Leu Phe Gly Leu Trp Glu Trp Ile Val Tyr Glu Cys  
 145 150 155 160  
 Leu Gly Ala Ile Leu Met Arg Val Asn Ser Cys Lys Asn Trp Leu Leu  
 165 170 175  
 Lys Arg Ala Trp His His Leu Leu Ser Leu Leu Pro Phe Ser Pro Thr  
 180 185 190  
 Met Cys Ser Ser Val Tyr Ala Ser Ser Leu His Leu Pro Pro Arg Val  
 195 200 205  
 Glu Ala Ser Leu Arg Leu His Gln Thr Gln Ile Leu Val  
 210 215 220

<210> 159  
 <211> 156  
 <212> PRT  
 <213> Homo sapiens

<400> 159

Phe Leu Ser Cys Trp Thr Gln Lys Arg Leu Pro Ser Arg Glu Thr Cys  
 1 5 10 15  
 Pro Gln Leu Phe Trp Val Lys Ala Cys Ala Gly Thr Tyr Asp Ser Lys  
 20 25 30  
 Ser Gln Leu Lys Trp Ile Ser Ile Ser Ser Ser Asn Ser Pro Ser

35                      40                      45  
 Leu Arg Lys Asn Ser Ser Phe Leu Cys Phe Ile Tyr Val Asn Ile Gly  
 50                      55                      60  
 Lys Arg Cys Met Tyr Asp Val Phe Phe Leu Phe Ile Ser Phe Cys Ser  
 65                      70                      75                      80  
 Asn Cys Lys Lys Ser His Met Phe Leu Val Lys Lys Ser Thr Asn Gln  
 85                      90                      95  
 Pro Thr Leu Lys Asn Leu Asn Asn Glu Gln Arg Glu Lys Lys Leu Pro  
 100                      105                      110  
 Asn Ile Lys His Asn Val Tyr Thr Leu Gln Lys Leu Glu Lys Tyr Arg  
 115                      120                      125  
 Lys Thr Gln Arg Lys Glu Lys Lys Ile Thr Ser Thr Gln Asn Tyr Phe  
 130                      135                      140  
 Cys Phe Gln Tyr Ile Ala Lys His Phe Ser Met Tyr  
 145                      150                      155  
 <210> 160  
 <211> 200  
 <212> PRT  
 <213> Homo sapiens  
 <400> 160  
 Phe Val Lys Lys Val Gln Ser Met Asn Leu Thr Gly Lys Ser Pro Leu  
 1                      5                      10                      15  
 Lys Ser Thr Cys Trp Leu Gly Asn Glu Lys Glu Val Glu Pro Gly Lys  
 20                      25                      30  
 Ala Thr Pro Ser Gly Tyr Ile Gly Lys Glu Ile Lys Ala Ala Thr Thr  
 35                      40                      45  
 Arg Gln Ser Glu Val Ala Gln Lys Trp Ser Met Phe Leu Arg Glu Leu  
 50                      55                      60  
 Leu Trp Phe Gly Tyr Gly Leu Ser Val Pro Thr Lys Pro His Val Asp  
 65                      70                      75                      80  
 Ile Phe Phe Pro Val Trp Gln Cys Glu Val Arg Pro Ser Gly Arg Cys  
 85                      90                      95  
 Leu Gly His Gly Gly Gly Ser Leu Met Asn Thr Cys Cys Ser Gln Val  
 100                      105                      110  
 Ser Glu Phe Leu Trp Gln Asp Ile Ser Ser Cys Gly Asn Gly Val Val  
 115                      120                      125  
 Ser Ser Arg Val Gly His Lys Ala Thr Cys Pro Ser His Val Ser Thr  
 130                      135                      140  
 Ser Pro Leu Thr Phe Ser Thr Met Phe Trp Gln His Arg Ser Leu Thr  
 145                      150                      155                      160  
 Arg Ser Ala Asp Ala Gly Thr Met Val Leu Ile Gln Pro Ala Glu Gln  
 165                      170                      175  
 Ala Lys Ile Tyr Phe Leu His Lys Leu Leu Ser Leu Arg Tyr Phe Phe  
 180                      185                      190

Phe Phe Phe Leu Arg Gln Ser Leu  
195 200

<210> 161  
<211> 191  
<212> PRT  
<213> Homo sapiens

<400> 161

Gln Cys Gly Asp Ser Gly Ser Arg Arg Val Lys Asn Glu Val Trp Val  
1 5 10 15  
Gly Lys Glu Trp Ser Gly His Asp Arg Leu Trp Asn Leu Phe Glu Val  
20 25 30  
Lys Leu Glu Val Leu Lys Asn Phe Asn Gln Ala Asn Gly Phe Leu Leu  
35 40 45  
Phe Ile Leu Ile Lys Asp Tyr Phe Asp Cys Ser Val Glu Asn Arg Val  
50 55 60  
Glu Arg Asn Arg Glu Val Arg Asn Leu Leu Leu Phe His Met Lys Met  
65 70 75 80  
Met Tyr His Cys Leu Leu Ser Ala Trp Gly Leu Cys Arg Glu Lys Trp  
85 90 95  
Pro Asn Ile Arg Tyr Lys Arg Glu Tyr Thr Cys Gln Asp Leu Leu Met  
100 105 110  
Asp Tyr Ile Leu Val Leu Ile Val Asn Leu Gln Phe Leu Asn Gly Glu  
115 120 125  
Leu Leu Leu Met Tyr Ala Val Phe Ile His Tyr Ser Arg Cys Val Leu  
130 135 140  
Gln Met Thr Glu Ile Leu Lys Cys Asn Leu Ile Lys Asn Leu Leu Ile  
145 150 155 160  
Ser His Ile Val Ser Tyr Asp Trp Glu Ile Gly Val Arg Thr Leu Gly  
165 170 175  
Lys Ala Val Ser Gln Ala Tyr Arg Leu Leu Asn Leu Val Leu Ile  
180 185 190

<210> 162  
<211> 76  
<212> PRT  
<213> Homo sapiens

<400> 162

Leu Val Ala Ala Ala Leu His Thr Arg Leu Pro Pro Pro Gln Gly Val  
1 5 10 15  
Pro Asp Cys Ser Pro Arg Pro Val Gln Gln Leu Glu Thr Met Ala Gly  
20 25 30  
Arg Ile Arg Gly Arg Arg Ala Tyr Cys Ser Lys Thr Phe Gly Thr Ile  
35 40 45  
Cys Phe Ile Pro Tyr Phe Phe Gln Leu His Cys Val Leu Leu Leu Leu  
50 55 60



Val Ile Phe Thr Lys Glu Asn Phe Phe Thr Leu Ile  
65 70 75

<210> 163  
<211> 155  
<212> PRT  
<213> Homo sapiens

<400> 163

Thr Pro Ala Trp Val Ile Glu Arg Asp Ser Val Ser Lys Lys Lys Arg  
1 5 10 15

Lys Lys Lys Val Met Leu Val Glu Ala Asn Ser Arg Leu Ile Tyr Ile  
20 25 30

Phe Lys Asn Ile Phe Leu Gly Asn Leu Ile His Ile Gln Tyr Arg Leu  
35 40 45

Ser Ser Leu Ser Thr Leu Tyr Leu Ile Leu Pro Val Lys Leu Cys Thr  
50 55 60

Ile Lys Val Met Ser Cys Phe Ser Ala Met Pro His Ala Gly Gly Thr  
65 70 75 80

Ser Phe Leu Thr Pro Thr Ser Phe Pro Gly Glu Pro Arg Cys Ala Lys  
85 90 95

Gly Trp Asp Ala Trp His Arg Met Pro Ala Ser Arg Cys Leu Asn Ala  
100 105 110

Pro Ala Val Ser Pro Gly Ala Lys Ser Tyr Ser Thr Val Ser Leu Pro  
115 120 125

Pro Ala Glu Asn Arg Ser Ala Trp Cys Ile Gln Ala Thr Lys Gly Ile  
130 135 140

Cys Thr Asp Met His Thr Ala Ser Ala Val Gly  
145 150 155

<210> 164  
<211> 193  
<212> PRT  
<213> Homo sapiens

<400> 164

Gly Leu Ile Glu Trp Asn Leu Glu Ala Gly Arg Thr Gly Glu Gly Leu  
1 5 10 15

Pro Val Phe Ala Ser Lys Val Ile Phe Ser Tyr Leu Cys Glu Val Leu  
20 25 30

Arg Asn Tyr Lys Asn His Pro Ser Tyr Tyr Lys Arg Asp Gln Asp Gln  
35 40 45

Gln His Phe Leu Lys His Arg Val Gly His Asp Lys Cys Pro Arg Arg  
50 55 60

Asp Asp Thr Arg Glu Glu Ser Gly Val Asn Leu Ser Val Leu Thr His  
65 70 75 80

Tyr Phe Ile Ser Asn Leu Leu Ala Ser Lys Ile Val Phe Phe Phe Cys  
85 90 95

Glu Ser Leu Ser Ser Phe Pro Leu Phe Thr Asn Asn Ser Tyr Pro Gln  
 100 105 110  
 Ser Leu Cys Leu Pro Ile Gly Cys Phe Leu Ser Lys Phe His Leu Gly  
 115 120 125  
 Leu Leu Leu Pro Pro Ser Arg Thr Leu Lys Ser Gln Ser Tyr Leu Ile  
 130 135 140  
 Gly Ser Leu Asn Ala Leu Cys Ile Phe Leu Val Thr Thr His Asn Asn  
 145 150 155 160  
 Tyr Asn Asp Lys Gln Lys Asn Phe Ile Ser Val Ser Leu Gly Glu Asp  
 165 170 175  
 Gly Trp Met Glu Pro Gln Lys Tyr Ala Arg Ile Thr Lys His Asn Leu  
 180 185 190

Asn

<210> 165  
 <211> 124  
 <212> PRT  
 <213> Homo sapiens

<400> 165

Phe Leu Ser Gly Ile Pro Leu Thr Gly Leu Arg Lys Ser Thr Gln Tyr  
 1 5 10 15  
 Ala Phe Leu Ser Ala Glu Asp Ser Asn Thr Ser Lys Ile Ile Leu Ile  
 20 25 30  
 Phe Leu Phe Ala Lys Val Tyr Leu Gln Lys Leu Phe Leu Gln Lys Leu  
 35 40 45  
 Lys Ser Arg Ser Gln Leu Ser Ile Phe Ile Val Leu Thr Ser Arg Leu  
 50 55 60  
 Thr Asn Gln Leu Leu Thr Pro Phe Pro Glu Lys Cys Phe Ala Leu Thr  
 65 70 75 80  
 Lys Val Glu Ile Leu Arg Leu Ile Cys Ser Ile Ser Trp Ile His Tyr  
 85 90 95  
 Ile Tyr Tyr Leu Ile Tyr Cys Ser Leu Val Val Cys Ile Cys His Tyr  
 100 105 110  
 Ser Glu Ile Gln Lys Lys Cys Ser Asn Leu Tyr Leu  
 115 120

<210> 166  
 <211> 230  
 <212> PRT  
 <213> Homo sapiens

<400> 166

Gln Leu Gly Ile His Thr Gln Ser Thr Gln Pro Gln Glu His Ser Lys  
 1 5 10 15  
 Gly Gln Glu Leu Lys Leu Thr Ser Arg Asp Gln His Leu Thr Lys Ser  
 20 25 30

His Val Met Asn Gln Lys Lys Lys Lys Lys Pro Lys Ser Lys Thr Phe  
 35 40 45  
 Asp Asn Arg Met Trp Cys Trp Asp Met Arg Gln Thr Val Val Ile Tyr  
 50 55 60  
 Ser Val Ile Tyr Arg Leu Pro Phe Thr Cys Arg Leu Ser Phe Tyr Phe  
 65 70 75 80  
 Asn Gln Met Leu Phe Gln Val Ile Ser Thr Leu Val Asn Gln Val Leu  
 85 90 95  
 Glu Ser Phe Ile Pro Arg Leu Cys Asn Thr Val Ile Ser Leu Ser Pro  
 100 105 110  
 Phe Leu Gly Gln Ala Asn Ser Leu Leu Ile Ser Leu Gly Trp Ile Leu  
 115 120 125  
 Lys Ser Asn Gln Ala Thr Asn Asp Leu Asp Cys Cys Tyr Phe Ser His  
 130 135 140  
 Leu Ala Ser Tyr Phe Leu Pro Leu Tyr Val Leu Phe Leu Ile Leu Ile  
 145 150 155 160  
 Leu Leu Phe Leu Lys Leu Val Lys Thr Ile Ser Pro Leu Gly Ser Leu  
 165 170 175  
 His Leu Ile Pro Leu Pro Arg Ile Leu Cys Pro Pro Asp Ile Asn Met  
 180 185 190  
 Val Tyr Tyr Phe Thr Ser Phe Glu Pro Ser Ser Asn Val Thr Phe Ser  
 195 200 205  
 Ile Lys Pro Thr Met Leu Val Ile Phe Tyr His Phe Leu Ser Asp Met  
 210 215 220  
 Ser Phe Ala Leu Tyr Cys  
 225 230

<210> 167  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<400> 167

Ile Thr Glu Asn Pro Phe Met Ala Ala Arg Arg Thr Trp Ile Phe Leu  
 1 5 10 15  
 Ile Phe His Trp Pro Trp Ser Gly Gly Thr Glu Pro Lys Ser Thr Trp  
 20 25 30  
 Gly Ala Gly Lys Ala Ala Val Arg Gly Arg Pro Cys Trp Cys Trp Pro  
 35 40 45  
 Cys Gln Pro Ala Leu Leu Val Ser Ile Ile Ala Leu Val Trp Gln Arg  
 50 55 60  
 Thr Leu Cys Asp Cys Glu Leu Arg Ser Ala Leu Arg Ser Leu Gln Ala  
 65 70 75 80  
 Ser Gly Leu Gln Val Pro Val Gln Pro Ser Ile Cys Phe Ser Pro Tyr  
 85 90 95

Val Arg Ser Thr Pro Thr Pro Val Tyr Thr Gly Ala Lys Cys Leu Leu  
 100 105 110  
 Arg Phe Trp Ala Phe His Gly Lys Val Leu Asn Val Phe Lys Tyr Leu  
 115 120 125  
 Lys Val Gln Leu Cys Met Leu Tyr Phe Ile Phe Ser Leu Lys Leu Glu  
 130 135 140  
 Thr Pro Tyr Thr Ser Ser Asn Lys Lys Ala Gln Gln Ala Leu Gly Phe  
 145 150 155 160  
 Ser Leu Ser Leu Leu Gly Pro Cys Thr Tyr Val Arg Phe Tyr Tyr Leu  
 165 170 175  
 Phe Gly Gly Val Asn Phe Thr Ala Phe Leu Ala Phe Met His Leu Glu  
 180 185 190

<210> 168  
 <211> 159  
 <212> PRT  
 <213> Homo sapiens

<400> 168

Leu Gln Ser Gly Lys Asn Asn Ile Gly Ser Lys Gly Ala Thr Lys Ile  
 1 5 10 15  
 Pro Gln Cys Leu Glu Arg Arg Lys Val Ser His Leu Ser Ser Asp Ser  
 20 25 30  
 Cys Gln Gly Ile Pro Leu Thr Gly Leu Arg Glu Ser Thr Gln Tyr Ala  
 35 40 45  
 Phe Leu Ser Ala Glu Asp Ser Asn Thr Ser Lys Ile Ile Leu Ile Phe  
 50 55 60  
 Leu Phe Ala Lys Val Tyr Leu Gln Lys Leu Phe Leu Gln Lys Leu Lys  
 65 70 75 80  
 Ser Arg Ser Gln Leu Ser Ile Phe Ile Val Leu Thr Ser Arg Leu Thr  
 85 90 95  
 Asn Gln Leu Leu Thr Pro Phe Pro Glu Lys Cys Phe Ala Leu Thr Lys  
 100 105 110  
 Val Glu Ile Leu Arg Leu Ile Cys Ser Ile Ser Trp Ile His Tyr Ile  
 115 120 125  
 Tyr Tyr Leu Ile Tyr Cys Ser Leu Val Val Cys Ile Cys His Tyr Ser  
 130 135 140  
 Glu Ile Gln Lys Lys Cys Ser Asn Leu Tyr Leu Tyr Lys Met Tyr  
 145 150 155

<210> 169  
 <211> 173  
 <212> PRT  
 <213> Homo sapiens

<400> 169

Arg Pro Pro Cys Leu Ser Glu Thr Ala Lys Met Val Ala Tyr Leu Ser  
 1 5 10 15

Leu Trp Pro His Pro Arg Glu Val Gly Asn Cys Cys Pro Glu Asn Thr  
                   20                                  25                                  30  
 Gly Gly Gly Gly His Arg Leu Trp Ser Gly Asn Ser Ala Trp Gly Arg  
                   35                                  40                                  45  
 Glu Leu Gly Pro Arg Thr His Val Lys Met Gln Ser Gly Cys Leu Ser  
                   50                                  55                                  60  
 Ile Glu Gln Leu His Cys Ser Gly Gly Leu Phe Gln Ser Leu Val Thr  
                   65                                  70                                  75                                  80  
 Ser Glu Ser Leu Glu Leu Lys Gly Asn Asn Gly Gly Cys Val Thr Ala  
                                   85                                  90                                  95  
 Lys Met Val Ala His Pro Ser His Arg Asp Leu His Pro Arg Glu Ala  
                   100                                  105                                  110  
 Gly Asn His Cys Asn Pro Glu Asn Thr Gly Gly Asp Trp Arg Ala Gln  
                   115                                  120                                  125  
 Ser Thr Val His Ala Glu Leu His Gly Ile Leu Ala Glu Gln Pro Leu  
                   130                                  135                                  140  
 Ile Trp Ser Pro Gly Gln Phe Arg Tyr Leu Gly Phe Pro Ala Lys Val  
                   145                                  150                                  155                                  160  
 Ala Ala Ile Ala Arg Leu Gly Val Arg Ser Pro Val His  
                                   165                                  170

<210> 170  
 <211> 228  
 <212> PRT  
 <213> Homo sapiens

<400> 170

Phe Pro Leu Gln Tyr His Val Leu Ser Glu His Pro Leu Leu Leu Lys  
   1                  5                                  10                                  15  
 Ser His His Asp Leu Ile Val Trp Asp Ile Phe Gly Leu Ala Leu Phe  
                   20                                  25                                  30  
 Cys Ser Phe Val Thr Phe His Thr Val Leu Ser Lys Thr His Gln Ser  
                   35                                  40                                  45  
 Ser Ser Leu His Trp Leu His Gly Cys Trp Ser Leu Cys Gly Leu Trp  
                   50                                  55                                  60  
 Gln Thr Thr Leu Ser Ile Pro Pro Leu Pro Gly Gln Asn Ser Asp Phe  
                   65                                  70                                  75                                  80  
 Val Arg Asp Ser Arg Val Pro Gly Lys Leu Asp Phe Leu Gly Ser Phe  
                                   85                                  90                                  95  
 Gly Val Lys Val Ala Lys Lys Leu Ser Pro Gly Gln Cys Phe Val Ser  
                   100                                  105                                  110  
 Arg His Leu Trp Ala Gly Leu Leu Glu Thr Leu Leu Phe Phe Trp Ser  
                   115                                  120                                  125  
 Gly Arg Val Leu Phe Ile Pro His Val Ser Leu Phe Trp Phe Gly Lys  
                   130                                  135                                  140  
 Arg Thr Thr Leu Ala Ala Phe Gln Lys Ala Glu Gly Ala Leu Ile Leu

145                      150                      155                      160  
 Lys Ser Leu Gln Thr Cys Cys Ser Met Gly Arg Thr Asp Leu Tyr Trp  
                                  165                                   170                                   175  
 Val Lys Pro Leu Trp Leu Ala Val Leu His Ala Ala Lys Tyr Asp Tyr  
                                  180                                   185                                   190  
 Tyr Val Arg Cys Phe Ser Glu Leu Ile Leu Ile Ala Lys Gln Phe Lys  
                                  195                                   200                                   205  
 His Val Trp Gly Leu Asn Gly Ile Arg Ala Gly His Gly Gly Ser Arg  
                                  210                                   215                                   220

Leu Ser Gln His  
 225

<210> 171  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

<400> 171

Leu Leu Ala Phe Ser Ile Asn Thr Glu Gly Ser Ile Arg Lys Tyr Ala  
 1                                   5                                   10                                   15  
 Leu Leu Trp Met Glu Ser Val Gln Cys Arg Leu Met Gly Phe Leu Ala  
                                  20                                   25                                   30  
 Met Leu Ser Thr Glu Val Ser Val Leu Leu Leu Thr Tyr Leu Thr Leu  
                                  35                                   40                                   45  
 Glu Lys Phe Leu Val Ile Val Phe Pro Phe Ser Asn Ile Arg Pro Gly  
                                  50                                   55                                   60  
 Lys Arg Gln Thr Ser Val Ile Leu Ile Cys Ile Trp Met Ala Gly Phe  
                                  65                                   70                                   75                                   80  
 Leu Ile Ala Val Ile Pro Phe Trp Asn Lys Asp Tyr Phe Gly Asn Phe  
                                  85                                   90                                   95  
 Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu Tyr Tyr Asp Gln Thr Glu  
                                  100                                   105                                   110  
 Asp Ile Gly Ser Lys Gly Tyr Ser Leu Gly Ile Phe Leu Gly Lys Leu  
                                  115                                   120                                   125  
 Tyr Phe Phe Ile Ser Trp Lys Asn Ile Ile Leu Leu Glu Ile Arg Ile  
                                  130                                   135                                   140  
 Ser Ala Lys Val Asp Leu Phe Val Ser Glu Ser Glu Ile Thr Ser Arg  
                                  145                                   150                                   155                                   160  
 Leu Cys Pro Phe Ser His Lys Lys Val Phe Thr Ile Val Phe Ile Glu  
                                  165                                   170                                   175  
 Val Leu Leu Asn Phe Leu Leu Asp Asn Ile Cys Gly Lys Arg His Thr  
                                  180                                   185                                   190

<210> 172  
 <211> 147  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 172

Cys Phe Ile Gly Cys Phe Ile Gly Leu Gln Arg Ile Phe Lys Arg Ile  
 1 5 10 15  
 Phe Gln Thr Arg Ile Phe Gln Asn Phe Ile Ser Leu Ile His Pro Leu  
 20 25 30  
 Phe Ile Tyr Phe Tyr Leu Cys Phe Gln Phe Pro Leu Ile Asp Arg Lys  
 35 40 45  
 Phe Thr Cys Ser Lys Met His Arg Thr Ser Val Tyr Asn Ser Ile Ile  
 50 55 60  
 Leu Asp Lys Tyr Val His Leu Gly Asn His Leu Asn Gln Asp Thr Glu  
 65 70 75 80  
 His Ser Gln His Ser Gly Lys Ile Leu Cys Val His Phe Ser Tyr Ala  
 85 90 95  
 Tyr Ser Tyr His Gln Pro Cys Phe Trp Phe Leu Leu Pro Tyr Ile Ser  
 100 105 110  
 Leu Ser Cys Pro Ile Ser Arg Lys Trp Asn His Thr Leu Cys Ser Leu  
 115 120 125  
 Leu Cys Leu Leu Glu Leu Asn Val Thr Phe Asp Ala Phe Tyr Ile Thr  
 130 135 140  
 Gly Cys Thr  
 145

&lt;210&gt; 173

&lt;211&gt; 197

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 173

Cys Ser Ser Ala Leu Met Asp Tyr Pro Phe Leu Val Lys Ile Thr Leu  
 1 5 10 15  
 Ile Asn Asn His Tyr Ser Gly Asn Tyr Leu Asn Thr Phe Ala Ser Val  
 20 25 30  
 Pro Arg Lys Asn Asn Tyr Phe Gln Asn Lys Lys Val Ala Lys Pro Pro  
 35 40 45  
 Pro Asn Pro Thr Lys Ile Ile Arg Ile Pro Arg Met Gly Leu Ile Ile  
 50 55 60  
 Ser Leu His Thr Asn Ser Ala Leu Ser Phe Ile Phe Lys Ser Val Arg  
 65 70 75 80  
 Glu Asn Ala Ala Ser Cys Leu Thr Phe Phe Val Cys Leu Thr Lys Lys  
 85 90 95  
 Leu Thr Ser Ile Val Lys Val Ile Leu Ile Trp Ser Leu Ser Leu Ser  
 100 105 110  
 His Tyr Val Gly Phe Asn Phe Leu Ser Gln Glu Asp Thr Ser Cys Ile  
 115 120 125  
 Leu Asp Leu Ser Ile Tyr Glu Gln Met Phe Tyr Phe Leu Ser Phe Lys  
 130 135 140

Asn Phe Leu Cys Trp Ile Asn Tyr Lys Thr Gln Thr Phe Leu Lys Gly  
145 150 155 160

Lys Tyr Leu Gly Phe Val Asn Ile Asn Phe Glu Asn Val Phe Phe Leu  
165 170 175

Ile Leu Leu Ile Leu Thr Leu His Pro Lys Tyr Leu Leu Tyr Phe Leu  
180 185 190

Gly Asp Ile Gln Val  
195

<210> 174

<211> 168

<212> PRT

<213> Homo sapiens

<400> 174

Leu Leu Lys Arg Leu Leu Thr Leu Ser Ser Ser Phe Leu Asn Gln Lys  
1 5 10 15

Ile Ser Tyr Cys Phe Tyr Leu Leu Arg Val Ser Leu Tyr Phe Ser Phe  
20 25 30

Gln Phe Met Leu Ile Ser Lys Leu Pro Cys Ile Ser Lys Gly Leu Ser  
35 40 45

Ile Tyr Thr Ile Lys Pro Leu Tyr Val Ser Lys Val Phe Ile Gly Asn  
50 55 60

Leu Gly Leu Tyr Asp Pro Lys Leu Cys Trp Ser Thr Thr Phe Ser Val  
65 70 75 80

Lys Tyr Leu Ala Ile Lys Tyr Arg Lys Lys Lys Ser Val Gly Gln Arg  
85 90 95

Glu Val Met Ile Val Tyr Leu Cys Asn Leu Ile Lys Asn Val Ser Leu  
100 105 110

Asn Leu Gln Ser Ile Val Thr Tyr Arg Gly Arg His Tyr Gly Gly Arg  
115 120 125

Gly Gly Arg Tyr Lys Val Glu Asn Phe Ser Arg Ala Ser Gln Ser Asn  
130 135 140

Lys Ile Gly Ile Tyr Lys Tyr Leu Leu Arg Arg Thr Leu Leu Ser Ala  
145 150 155 160

Lys Ile Val Ala Gln Arg Ala Ile  
165

<210> 175

<211> 164

<212> PRT

<213> Homo sapiens

<400> 175

Gly Gly Gly Gln Glu Ser Tyr Tyr Thr Ile Ile Glu Cys Ser Lys Ser  
1 5 10 15

Asp Leu Ala His Ser His Met Asn Asp Leu Leu Leu Ile Thr Lys Phe  
20 25 30



Cys Val Leu Ile His Lys Gln Arg Asn Leu Thr Ile Asn Lys Arg Ile  
           35                  40                  45  
 His Tyr Pro Ala Asn Val Ile Leu Cys Thr Val Gln Ser Ile Thr Asp  
           50                  55                  60  
 Leu Asn Glu Pro Tyr Val Val Glu Cys Leu Ile Met His Phe Ser Ile  
   65                  70                  75                  80  
 Val Tyr Gly Leu Asn Lys Leu His Ile Thr Tyr Lys Ser His Trp Leu  
                   85                  90                  95  
 Leu Tyr Thr Leu Val Asn Cys Lys Pro Lys His Ser Arg Leu Gly Asn  
           100                  105                  110  
 Lys Tyr Thr Phe Leu His Lys Asn Ser Ile Ala Ser Gly Ala Val Leu  
           115                  120                  125  
 Pro Val Trp Phe Thr Leu His Pro Asp Thr Ser Asn Tyr Thr Val Leu  
           130                  135                  140  
 Asn Glu Ser Leu Cys Ser His Ile Asn Lys Leu Ser Pro Phe Asn Phe  
   145                  150                  155                  160  
 Ser Tyr Asn Lys

<210> 176  
 <211> 186  
 <212> PRT  
 <213> Homo sapiens

<400> 176

Thr Ala Leu Leu Tyr His Arg Asp Met Pro Gly Asn Ser Ser His Gln  
   1                  5                  10                  15  
 Met Leu Ser Gly Gly Val Pro Met Arg Lys Arg Pro Gln Val Ser Gln  
           20                  25                  30  
 Thr Ala Gln Arg Tyr His Asp Asp Gly Arg Leu Phe Pro Trp Cys Leu  
           35                  40                  45  
 Gly Arg Leu Leu Ser Phe Ile Thr His Leu Phe Arg Arg Glu Val Thr  
           50                  55                  60  
 Met Gln Arg Gly Cys Leu Val Leu Leu Pro Gly Cys Lys Pro Trp Gly  
   65                  70                  75                  80  
 Pro His Ser His Pro Trp Glu Gln Arg Met Trp Glu Gln Asn Phe Arg  
           85                  90                  95  
 Cys Ser Asn Ser Lys Gly Ala Trp Pro Leu Ser Val Ser Leu Pro Glu  
           100                  105                  110  
 Ser Arg Ala Gln Ala Lys Thr Gln Ala Pro Ser Arg Pro Leu Trp Gln  
           115                  120                  125  
 Val Thr Thr Ser Leu Pro Thr Thr Ile Thr Ser Pro Pro Tyr Gln Gln  
           130                  135                  140  
 Ile Leu Asp Ser Leu Gln Leu Pro Ile Lys Gly Lys Pro Pro Lys Ala  
   145                  150                  155                  160

Lys Pro Asp Phe Pro Ile Leu Lys Cys Leu Asn Arg Glu Gly His Ser  
 165 170 175

Gly Phe Met Ser Ile Ile Pro Ala Phe Glu  
 180 185

<210> 177  
 <211> 217  
 <212> PRT  
 <213> Homo sapiens

<400> 177

Ala Ala Phe Ser Ala Leu Pro Arg Val Leu Cys Gly Pro Pro Glu Val  
 1 5 10 15

Gln Leu Val Ser His Gly Leu Val Phe Thr Ala Met Leu Phe Asp  
 20 25 30

Ala Ile Lys Thr Ser His Cys Gln Ser Ala Cys Phe Leu Leu Gly Ala  
 35 40 45

Ser Phe Leu Thr Arg Arg Ser Gln Lys Pro Arg Pro Gly Gly Asp Leu  
 50 55 60

Ser Arg Leu Thr Ser Gly Val Gly Thr Leu Cys Pro Ser Ser Val Phe  
 65 70 75 80

Leu Glu His Pro Gly Glu Pro Ala Ala Arg Arg Ser Pro Thr Ala Gly  
 85 90 95

His Val Glu Ala Asn Ser Pro Pro Thr Gln Thr Ala Trp Ala Met Leu  
 100 105 110

Lys Arg Ala Ser Ala Pro Asn Asp Phe Ser Glu Val Gln Thr Ser Pro  
 115 120 125

Arg Leu Ser Ala Ser Glu Ser Leu Pro Leu Gln Pro Arg Pro Leu His  
 130 135 140

Gly Gly Arg Gly Gly Asp Thr Gln Lys Phe Gly Phe Phe Gly Ala Ala  
 145 150 155 160

His Thr Gln Asp Val Ser Gly Ala Gly Lys Gly Ser Lys Trp Ser Leu  
 165 170 175

Cys Arg Asn Thr Cys Ala Arg Leu His Gly Phe Thr Thr Thr Arg Arg  
 180 185 190

Gln Leu Lys Ile Pro Thr Thr Pro Gly Val Ser Trp Leu Val Ser Arg  
 195 200 205

Ser Leu Thr His Gly Thr Ala Leu Thr  
 210 215

<210> 178  
 <211> 187  
 <212> PRT  
 <213> Homo sapiens

<400> 178

Lys Tyr Asn Tyr Ile Ser Ile Tyr Met Tyr Ser Leu Arg Asn Asn Lys  
 1 5 10 15

Met Asn Ile His Val Phe Ser Leu Pro Ser Phe Phe Phe Leu Ile Pro  
 20 25 30  
 Cys Ile Gln Phe Glu Ala Phe Lys Asn Phe Ile Phe Leu His Leu Tyr  
 35 40 45  
 Leu Met Leu Leu Ala Thr Leu Gly Tyr Phe Leu Ser Pro Ile Leu Ile  
 50 55 60  
 Phe Gly Cys Ser Tyr Ile Ser Ile Ile Lys Arg Glu Ser Asp Val Gly  
 65 70 75 80  
 His Ser Tyr Ser Val Val Cys Asn Leu Asn Tyr Ser Glu Ile Ser Arg  
 85 90 95  
 Val Leu Ser Leu Pro Ser Met Leu Gln Val His Cys Cys Gly Ser Asn  
 100 105 110  
 Met Asp His Phe Cys Ser Phe Cys Ile Ser Ile Tyr Asp Asn Gln Tyr  
 115 120 125  
 Leu Ser Ile Leu Ile Gln Ile His Lys Tyr Phe Ser Gly Pro Leu Asn  
 130 135 140  
 Leu Lys Ile Cys Leu Leu Lys Thr Leu Ile Ser Phe Glu Tyr Asp Cys  
 145 150 155 160  
 Pro Thr Phe Leu Phe Gly Phe Leu Leu Gly Lys Phe Val Leu Asp Arg  
 165 170 175  
 Cys Trp Glu Leu Trp Asp Ile Cys Leu His Val  
 180 185

<210> 179  
 <211> 115  
 <212> PRT  
 <213> Homo sapiens

<400> 179

Leu Ile His Thr Leu Cys Ala Ile Val Cys Asn Ser Asn Thr Gln Arg  
 1 5 10 15  
 Cys Lys Phe Glu Ser Phe Ser Thr Leu Ala Ala Tyr Trp Asn Tyr Pro  
 20 25 30  
 Gly Val Phe Thr Ile Ser Asp Ile Gln Val Ile Val Leu His Ser Lys  
 35 40 45  
 Thr Glu Asn Ser Ala Phe Asp Leu Tyr Glu Cys Leu Pro Pro Val Leu  
 50 55 60  
 Ser Phe Phe Tyr Pro Leu Gln Gln Thr Thr Lys Leu Ser Ile Phe Ile  
 65 70 75 80  
 Leu Leu Ala Gly Phe Lys Leu Gln Ala Ile Val Trp Leu Arg Lys Phe  
 85 90 95  
 Asn Tyr Tyr Thr Phe Ile Glu Cys Thr Leu Ile Cys Gln Glu Ile Gly  
 100 105 110  
 Gln Ile Lys  
 115

<210> 180

<211> 196  
 <212> PRT  
 <213> Homo sapiens

<400> 180

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Leu Leu Met Gln Leu Pro Lys Thr Leu Phe Lys Ile Val Ser Asn Lys
1           5           10           15

His Glu Cys Ser Glu Asn Ser Leu Glu Thr Leu Ile Arg Lys Trp Pro
20           25           30

His Ser Arg His His Cys Gly Ile Ser Thr Lys Trp Asp Ser Gly Asp
35           40           45

Glu Glu Phe Ser His Glu Arg Arg Gln Leu Pro Asn Glu Val Glu Arg
50           55           60

Lys Asp Val Glu Ser Leu Gln Asn Asn Ser Pro Leu Ser Leu Met Lys
65           70           75           80

Gly Lys Asn Ser Gln Asn Ser Thr Ala Glu His Glu Thr Asn Leu Asn
85           90           95

Tyr Phe Arg Ala Met Asn Lys Ile Asn Ser Ile Thr Phe Ile Leu Cys
100          105          110

Pro Gln Phe Phe Gln Val Asn Tyr Leu Leu Ala Phe Asp Tyr Tyr Phe
115          120          125

Val Ser His Lys Ile Cys Tyr Glu Ser Met Tyr Arg Ile Leu Ser Asp
130          135          140

Trp Leu Cys Tyr Cys Asn Gln Arg Cys Val Asp His Pro Val Gln Cys
145          150          155          160

Trp Gln Asp Ile Pro Tyr Ile Met Asn Phe His Ser Pro Leu Leu Ala
165          170          175

Val Cys Gly Leu Thr Asn Lys Tyr Ser Ile Leu Ile Leu Gln Ala Ile
180          185          190

Arg His Phe Ala
195

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<210> 181  
 <211> 216  
 <212> PRT  
 <213> Homo sapiens

<400> 181

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Lys Trp Asp Ser Ile Phe Arg Asn Val Cys Ile Leu Tyr Asp Phe Gly
1           5           10           15

Asn Leu Arg Lys Tyr Gly Arg Lys Lys Asn Leu Ile Leu Phe Ser Asp
20           25           30

Asn Cys Gly Tyr Ser Phe Lys Pro His Lys Ser Leu Thr Asn Arg Ile
35           40           45

Phe Ser Lys Val Ser Tyr Asn Val Glu Ser Val Thr Val Leu Met Thr
50           55           60

Phe Phe Val Leu Cys Tyr Ile Lys Ile Ser Ser Val Leu His Leu Asp

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65                      70                      75                      80  
 Arg Asn Phe Phe Ala Ser Phe Cys Thr Ser Leu His Glu Leu Phe Gly  
                                  85                      90                      95  
 Asn Tyr Leu Thr Asp Leu Cys Ser Tyr Lys Cys His Val Ser Leu Tyr  
                                  100                      105                      110  
 Asn Ile Lys Ile Ala Phe Val Asn Ile Ile Ile Thr Leu Ala Ser Lys  
                                  115                      120                      125  
 Asp Trp Asp Ala Asn Lys Leu Thr Val Asp Ala Thr Phe Phe Pro Lys  
                                  130                      135                      140  
 Leu Glu Phe Cys His Trp Gln His Ile Leu Pro Val Ile Phe Leu Glu  
                                  145                      150                      155                      160  
 Val Thr Gly Leu Cys Tyr Phe Leu Lys Arg Met Cys Ala Lys Tyr Pro  
                                  165                      170                      175  
 Ser Leu Ser Asn His Ser Ser Ser Val Ser Gly Phe Leu Ser Gly Asn  
                                  180                      185                      190  
 Asp Val Pro Leu Lys Lys Val Ala Asn Ser Ser His Asn Ser Ile Val  
                                  195                      200                      205  
 Val Leu Phe Leu Glu Val Thr Ile  
                                  210                      215  
 <210> 182  
 <211> 182  
 <212> PRT  
 <213> Homo sapiens  
 <400> 182  
 Pro Ser Pro Gln Phe Asn Tyr Leu Pro Pro Cys Pro Ser His Asn Thr  
                                  5                      10                      15  
 Trp Glu Phe Lys Val Arg Ser Glu Trp Gly Gln Ser Glu Thr Ile Leu  
                                  20                      25                      30  
 Ile Ile Ser Asp Cys Lys Leu Tyr Glu Ala Lys Lys Tyr Val Phe Cys  
                                  35                      40                      45  
 Ser Pro Leu Tyr Leu Lys His Leu Ala Tyr Leu Ala Asn Arg Cys Leu  
                                  50                      55                      60  
 Met Asn Tyr Leu Phe Asn Gly Cys Ser Phe Val Leu Val Thr Leu Gln  
                                  65                      70                      75                      80  
 Gly His Phe Phe Pro Cys Gly His Gly Gln Thr Val Leu Trp Leu Val  
                                  85                      90                      95  
 Ala Val Met Met His Gly Ser Thr Gly Val Leu Pro Thr Gly Leu Leu  
                                  100                      105                      110  
 Lys Thr Ile Asn Asn Phe Ser Ile Ser Ala Asn Arg Asn Leu Ile Tyr  
                                  115                      120                      125  
 Phe Cys Leu Trp Leu Cys Phe Leu Phe Phe Arg Ala Gln Ser Pro Ile  
                                  130                      135                      140  
 Cys Leu Lys Leu Phe Phe Phe Ser Phe Ala His Ile Leu Asn Gln Phe  
                                  145                      150                      155                      160

Leu Val Tyr Gln Ile Ser Thr Glu Asp Cys Thr Gln Asp Gly Arg Pro  
 165 170 175

Lys His Thr Cys Ser Thr  
 180

<210> 183  
 <211> 196  
 <212> PRT  
 <213> Homo sapiens

<400> 183

His Thr Tyr Leu Tyr Phe Pro Pro Ala Val Thr Leu Lys Phe Ser Gln  
 1 5 10 15

Leu Arg Gln Gln Ile Asp Phe Ile Ser Leu Ser Pro Leu Gln His Gln  
 20 25 30

Ile Lys Ala Phe Phe Leu Gly Thr Thr Leu Cys Leu Ser Asp Trp Leu  
 35 40 45

Ser Val Leu Arg Ala Thr Val Pro Arg Pro Asn Pro Trp Pro Ser Ser  
 50 55 60

Thr Gln Glu His Ser Gly Lys Gly Met Pro Phe Asn Phe Gln Ala Cys  
 65 70 75 80

Thr Asn Pro Gly Leu Trp Thr Arg Arg Arg Tyr Leu Trp Met Asn Arg  
 85 90 95

Gly Ser Ser Lys His Phe Ser Cys Arg Phe Tyr Ser Asn Pro Glu His  
 100 105 110

Ile Leu Cys Val Ala His Arg Ile Phe Phe Leu Phe Asn Ser Val Asp  
 115 120 125

Leu Met Ile Thr Arg Phe Ser Ala Val Asp Cys Gly Pro Tyr Pro Leu  
 130 135 140

Cys Leu His Ile Tyr Phe Ser Lys Trp Lys Asp Val Ser Arg Thr Val  
 145 150 155 160

Lys Lys Ile Ile Phe Thr Leu Asn Ile Leu Phe Leu Pro Asp Thr Ser  
 165 170 175

Phe Ser Ile Val Leu Leu Thr Ile Leu Lys Ser Asn Gln Asn Leu Asn  
 180 185 190

Phe Gln Tyr Ile  
 195

<210> 184  
 <211> 139  
 <212> PRT  
 <213> Homo sapiens

<400> 184

Leu Leu Ala Ile Asn Phe Trp Gly Glu Lys Gly Gln Asn Arg Asn Arg  
 1 5 10 15

Ala Thr Gln Glu Val Lys Phe Lys Trp Ile Asn Trp Ser Leu Leu Asn  
 20 25 30

Gln Gln Ile Cys Cys Lys Gln Asn Arg His Ser Met Met Pro Cys Ile  
 35 40 45  
 Val Leu Phe Asn Ile Thr Leu Leu Ile Ser Arg Val Cys Val Cys Val  
 50 55 60  
 Cys Val Cys Val Ser Cys Val Leu Thr Tyr Tyr Gly Ser Thr Ser His  
 65 70 75 80  
 Ala Thr Ser Leu Ala Leu Leu Leu Ser Arg Glu Cys Arg Gly Leu Leu  
 85 90 95  
 Val Leu Ser Ala Met Phe Asn Ser Ala Ser Thr Met Ile Gly Phe Gln  
 100 105 110  
 Ile Gln Lys Asn Ala Phe Leu Cys Ile Arg Asn Pro Asn His His Lys  
 115 120 125  
 Asn Ile Gln Lys Arg Met Asn Ile Phe Leu Leu  
 130 135

<210> 185  
 <211> 204  
 <212> PRT  
 <213> Homo sapiens

<400> 185

Phe Pro Ser Leu Gly Ile Tyr Cys Glu Val Leu Leu Val Thr Phe Ser  
 1 5 10 15  
 Lys Val Ile Gly Thr Ser Pro Ala Thr Ile Ser Ser Phe Ser Phe His  
 20 25 30  
 Val Cys Leu Cys Ser Phe Leu Ser Cys Gln Lys His Leu Lys Cys Ile  
 35 40 45  
 Ile Phe Thr Leu Cys Cys Phe Cys Tyr Cys Lys Ser Asn Phe Lys Val  
 50 55 60  
 Ile Cys Thr Pro Val Leu Phe Leu Gln Lys Tyr Phe Leu Val Leu Asn  
 65 70 75 80  
 Asp His Asn Lys Arg Val Gly Gly Asp Phe Thr Thr Gly Lys Ile Thr  
 85 90 95  
 Gln His Glu Lys Ala Ala Phe Val Asn Leu Ser Phe Asn Arg Ala Ala  
 100 105 110  
 Pro Val Ile Leu Thr Glu Thr Lys Val Lys Tyr His Cys Val Thr Arg  
 115 120 125  
 Leu Phe Val Thr Asn Met Ser Ile Asn Ile Asn Ala Met Ala Ala Leu  
 130 135 140  
 His Ser Gly Gly Gly Val Trp Cys Trp Val Ala Ala Gln Ile Thr Tyr  
 145 150 155 160  
 Ile Asn Asn Ser Gln Ser Gln Leu Cys Asn Ile Ile Lys Ala Leu Leu  
 165 170 175  
 Lys Tyr Val Ser Val Pro Glu His His Pro Ser Glu Ile Leu Ile Gln  
 180 185 190

Leu Ile Leu Pro Val Lys Glu Ser Ile His Thr Phe  
195 200

<210> 186  
<211> 170  
<212> PRT  
<213> Homo sapiens

<400> 186

Cys Leu Asn Val Leu Arg Lys Leu Cys Ala Gln Lys Gln Thr Tyr Ser  
1 5 10 15  
Gly Leu Met Val Cys Ser Thr His Thr His Thr Lys Trp Pro Phe Ser  
20 25 30  
Gln Ser Ser Trp Leu Ser Ser Thr Ser Pro Cys His Thr Cys Ile Gln  
35 40 45  
Ile Thr Leu Ser Val Ile His Cys Arg Asn Leu Ile Asn Lys Lys Ser  
50 55 60  
Leu Val Ile Thr Gly Pro Ser Leu Ala Phe Phe Tyr Trp Pro Asn Ala  
65 70 75 80  
Glu Tyr Phe Trp Leu Glu Met Ile Thr Leu Phe Ala Glu Ser Arg Leu  
85 90 95  
Ala Leu Gly Leu Met Ile Leu Ser Ser Cys His Ser Leu Phe His Ile  
100 105 110  
His Trp Arg Arg Leu Phe Pro Gly Glu Gly Ala His Asn Cys Ala Cys  
115 120 125  
Leu Phe Gln Asp Val Ser Leu Gly Thr Met Leu Gly Ser Asp Phe Pro  
130 135 140  
Arg Val Arg Ser Ala Leu Cys Leu Ala Phe Trp Leu His Pro Cys Ala  
145 150 155 160  
Gln Arg Arg Asp Arg Val Lys Glu Leu Arg  
165 170

<210> 187  
<211> 216  
<212> PRT  
<213> Homo sapiens

<400> 187

Leu Leu Thr Lys Pro Ser Phe Asn Val Asn Ala Leu His Cys Ile Ile  
1 5 10 15  
His Tyr Ile Ile Asn Asn Pro Cys Val Cys Val Cys Val Cys Val Cys  
20 25 30  
Val Cys Val Leu Thr Tyr Tyr Gly Ser Thr Ser His Ala Thr Ser Leu  
35 40 45  
Ala Leu Leu Leu Ser Arg Glu Cys Arg Gly Leu Leu Val Leu Ser Ala  
50 55 60  
Met Phe Asn Ser Ala Ser Thr Met Ile Gly Phe Gln Ile Gln Lys Asn  
65 70 75 80



Ala Phe Leu Cys Ile Arg Asn Pro Asn His His Lys Asn Ile Gln Lys  
                     85                    90                    95

Arg Met Asn Ile Phe Leu Leu His Phe Phe Val Val His Tyr Leu Asp  
                     100                    105                    110

Phe Ile Ile Ile Ile Leu Arg Lys His Leu Glu Lys Leu Gly Asn Val  
                     115                    120                    125

Ala Ala Leu Phe Ile Lys Glu Gly Lys Gly Glu Thr Arg His Leu Lys  
                     130                    135                    140

Ser Lys Ile Arg Asn Asp Phe Arg Thr Asn Ile Phe Asn Asn Leu Ser  
                     145                    150                    155                    160

Val Arg Glu Lys Phe Trp Tyr Phe Leu Lys Thr Ile Cys Leu Cys Ile  
                     165                    170                    175

Arg Pro Phe His Leu Asp Tyr Arg Gln Ile Met Cys Lys Phe Ile Ser  
                     180                    185                    190

Val Lys Thr Val Lys Asp Arg Leu Leu Pro Glu Pro Leu Asn Ile Phe  
                     195                    200                    205

Leu Ser Lys Phe Arg Asp His Phe  
                     210                    215

<210> 188  
 <211> 146  
 <212> PRT  
 <213> Homo sapiens

<400> 188

Cys Gly His Cys Gly Ala Gly Ser Leu Gly Phe Ser His Ser Thr Gln  
   1                    5                    10                    15

Gln Val Val Ser Val Val Asp Asn Tyr Glu Val Phe Tyr Met His Arg  
                     20                    25                    30

Ile Ile Leu Asp Thr Leu Gly Lys Leu Tyr Lys Lys Asn Arg Phe Tyr  
                     35                    40                    45

Phe Val Ser Tyr Thr Asp Asp Ile Ile Lys Thr Lys Thr Thr Asn Leu  
                     50                    55                    60

Ala Arg Gly Gly Asp Asn Glu Asn Leu Ser Leu Leu Tyr Gln His Leu  
                     65                    70                    75                    80

Gln Ala Tyr Phe Val Tyr Leu His Phe Ala Leu Leu Cys Phe Ile Asp  
                     85                    90                    95

Ile Ala Tyr Phe Thr Asn Arg Thr Thr Ala Thr Leu His Arg Ala Ser  
                     100                    105                    110

Phe Leu Glu Pro Phe Leu Gln His His Val Leu Thr Ser Cys Leu Cys  
                     115                    120                    125

Tyr Phe Leu Gln Tyr Phe Pro Phe Tyr Tyr Tyr Cys Val Cys Asp Asn  
                     130                    135                    140

Leu Ser  
 145

<210> 189

<211> 206  
 <212> PRT  
 <213> Homo sapiens

<400> 189

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Leu Gly Leu Gln Ala Ala Thr Ala Thr Gly Leu His His Cys Phe Lys
1          5          10          15
Ser Phe Leu Ser Ile Val Pro Arg Cys Ile Leu Asp Asn Phe Gln Glu
20          25          30
Gly Asp Leu Leu Asp Ser His Lys Arg Phe Val Leu Cys Trp Gln Leu
35          40          45
Ser Ile Lys Ser Leu Ala Lys Pro Pro Leu Tyr Thr Ala Thr Val Gly
50          55          60
Thr Ile Val Asn Tyr Cys Leu Pro Gly Ile Met Ile Arg Gln Pro Tyr
65          70          75          80
Ile Tyr Phe Cys Ile Phe Asn Leu Tyr Ile Leu Arg Ile Ser Asp Tyr
85          90          95
Ile Gly Tyr Tyr Thr Val Cys Ile Cys Thr Asn His Leu Ile Ser Phe
100         105         110
Lys Val Ile Val Leu Gly Ile Lys Met Asn Cys Ser Asn Ile Tyr Ile
115         120         125
Phe Lys Cys Thr Glu Ser Arg Tyr Thr Glu Leu Phe Arg Ile Phe Phe
130         135         140
Leu Leu Gly Ile Ala Leu Ser Ile Phe Thr Ile Pro Val Ile Cys Ile
145         150         155         160
Leu Tyr Tyr Phe Val Ser Asn Asn His Ile Leu Phe Asp Asp Met Val
165         170         175
Met Leu Phe Phe Ile Val Lys Trp Trp Ser Pro Gly Arg Ala Gln Trp
180         185         190
Leu Thr Pro Pro Asn Pro Gln His Phe Gly Arg Pro Arg Arg
195         200         205

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<210> 190  
 <211> 212  
 <212> PRT  
 <213> Homo sapiens

<400> 190

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Ile Ser Pro Glu Pro Thr Lys Arg Asp Lys His Ser Val Val Phe Phe
1          5          10          15
Ser Ala Leu Ile Gln Leu Cys Cys Lys Phe Leu Phe Ser Glu Glu Thr
20          25          30
Pro Arg Ser Met Thr Glu Ile Phe Phe Pro Phe Pro Phe Cys Asp Val
35          40          45
His Leu Ser Ile Leu Asp Ala Cys Thr Pro Glu Leu Thr Ser His Ser
50          55          60
Glu His Ala Gln His His Thr Leu Pro Ser Ser Pro Ala Arg Thr Val

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65                      70                      75                      80  
 His Ser Ser Ser Cys Val Asn Pro Trp Leu Ser Phe Leu Phe Arg Thr  
                                  85                      90                      95  
 Ala Phe Gln Ala Pro Trp Thr Leu Thr Leu Thr Ser Tyr Ala Gln Lys  
                                  100                      105                      110  
 Arg Leu Trp Glu Thr Glu Val Thr Ile Ser Gly Phe Arg Met Ala Phe  
                                  115                      120                      125  
 Phe Cys Ser Arg Lys Glu Pro Ala Val Pro Gln Val Leu Phe Leu Val  
                                  130                      135                      140  
 Pro Tyr Ser Ser Ala Pro Leu Arg Ile Lys Glu Val Gly Thr Val Ser  
                                  145                      150                      155                      160  
 Ser Leu Tyr Ser Tyr Ile Ile Glu Ser Asn Tyr Phe Cys Asn Leu Leu  
                                  165                      170                      175  
 Ser Ser Ser Gly Tyr Tyr Met Asn Glu His Ser Val Pro Phe Ile Asp  
                                  180                      185                      190  
 Leu Leu Ser Gly Tyr Ile Leu Ala Phe Asn Ile Leu Tyr Leu Leu His  
                                  195                      200                      205  
 Tyr Leu Gly Leu  
                                  210

<210> 191  
 <211> 201  
 <212> PRT  
 <213> Homo sapiens

<400> 191

Leu Leu Ser Pro Gln Pro Pro Lys Glu Leu Arg Leu Pro Thr Asn Val  
 1                      5                      10                      15  
 Pro Ser Ile Phe Lys Thr Leu Ser Trp Tyr Thr Asp His Asn Asn Ser  
                                  20                      25                      30  
 Tyr Ile Ile Val Asn Leu Ser Pro Phe Ile Cys Asn Ser Pro Gly Phe  
                                  35                      40                      45  
 Pro Cys Ser Phe Tyr Met Ser Lys Ala Pro Leu Glu Tyr Ile Thr Phe  
                                  50                      55                      60  
 Ser Ser Cys Ile Phe Gly Ser Tyr Leu Gln Phe Leu Thr Leu Pro Leu  
                                  65                      70                      75                      80  
 Phe Leu Lys Thr Leu Thr Phe Leu Arg Ile Thr Gly Gln Val Phe Tyr  
                                  85                      90                      95  
 Arg Met Ala Phe Ser Trp Tyr Phe Cys Leu Met Val Phe Ser Leu Ala  
                                  100                      105                      110  
 Trp Gly Lys Val Phe Trp Glu Glu Asp Ser Arg Asp Glu Glu Val Leu  
                                  115                      120                      125  
 Phe Ile Ser Pro Pro Ile Lys Val His Ala Val Asn Ile Thr Asn His  
                                  130                      135                      140  
 Cys Cys Pro Trp Ser Ala Gly Leu Arg Ser Tyr Leu Ser Gly Cys Phe  
                                  145                      150                      155                      160

Thr Met Asn Phe Phe Ser Phe Val Leu Pro Phe Tyr Thr Thr Leu Ser  
165 170 175

Gly Lys Thr Ile Thr Met Asp Ser Leu Tyr Leu Arg Asn Gly Asn Tyr  
180 185 190

Gly Leu Pro Leu Ile Tyr Arg Leu Phe  
195 200

<210> 192  
<211> 180  
<212> PRT  
<213> Homo sapiens

<400> 192

Ser Ala Ser Thr Leu Leu Tyr Cys Thr Pro Leu Asn Pro Cys Gln Thr  
1 5 10 15

Gln Gly Ile Ile Asn Ser Gln Ile Ala Pro Ser Ala Ser Ala Phe Lys  
20 25 30

Val Gln Tyr Phe Ser Arg Val Ala Asn Lys Leu Thr Thr Cys Pro Lys  
35 40 45

Thr Thr Glu Ile Tyr Ser Leu Ile Val Trp Arg Pro Lys Ser Arg Trp  
50 55 60

Trp Gln Gly Cys Ile Leu Ser Lys Gly Ser Ile Pro Cys Phe Phe Gln  
65 70 75 80

Leu Leu Met Ala Pro His Ile Pro Trp Leu Val Ala Thr Ser Leu Ser  
85 90 95

Tyr Leu Pro Trp Trp Ser His Gly Leu Leu Leu Phe Val Leu Phe Ser  
100 105 110

Val Ser Phe Phe Tyr Lys Asp Ile Cys His Trp Ile Ser Pro Pro Arg  
115 120 125

Lys Phe Arg Ile Ile Leu Pro Asp Ser His Leu Gln Pro Phe Glu Gly  
130 135 140

Leu Pro Ser Leu Phe Phe Phe Pro Tyr Lys Ile Thr Phe Thr Gly Ser  
145 150 155 160

Gly Asn Leu Asp Met Asp Ile Phe Trp Val Glu Lys Gly Thr Ile Pro  
165 170 175

Asn Thr Ala Cys  
180

<210> 193  
<211> 176  
<212> PRT  
<213> Homo sapiens

<400> 193

Pro Phe Asn Glu Met Ser Ile Ile Tyr Leu Asn Ile Ser Leu Asp Ser  
1 5 10 15

Lys Leu Gln Val Tyr Leu Gln Val Leu Ile Ser Leu His Phe His Asn  
20 25 30

Tyr Phe Ile Leu Ile Val Tyr Leu Asp Tyr Leu Arg Asn Leu Gln Leu  
 35 40 45  
 Ser Phe Asn Val Thr Phe Leu Ser Thr Ile Leu Leu Val Asp Phe Arg  
 50 55 60  
 Cys Leu Pro Val Arg Thr Leu Ser Leu Asp Thr Leu Phe Tyr Lys Ile  
 65 70 75 80  
 Ile Gln Val Leu Ala Ile Phe Ile Lys Pro Ile Leu Met Ser Tyr Leu  
 85 90 95  
 Ser Lys Ile Thr Gln Ala Lys Val Ile Ser Val Leu Val Trp Val Tyr  
 100 105 110  
 Ile Leu Ile Thr Leu Ile Ser Asn Phe Asp Pro Leu Tyr Phe Gly Arg  
 115 120 125  
 Asp Thr Tyr Ser Leu Leu Thr Pro Glu Lys Gly Val Leu Gln Arg Asn  
 130 135 140  
 Lys Leu Trp Met Ser Thr Lys Leu Gly Arg Leu Lys Ile Leu Arg Lys  
 145 150 155 160  
 Arg Gly Ala Pro Lys Leu Gln Gln Phe Val Leu Leu Ile Ala Ile Lys  
 165 170 175

<210> 194  
 <211> 88  
 <212> PRT  
 <213> Homo sapiens

<400> 194

Ser Tyr Val Phe Cys Gln Pro Ser Leu Asn Cys Gly Lys Leu Ile Cys  
 1 5 10 15  
 Leu Ala Asn Ser Val Lys Pro Tyr Thr Leu Tyr Ser Ser Gln Leu Tyr  
 20 25 30  
 Phe Gln Gln Gln Asn Asp Leu Met Arg Lys Ala Ala Leu Thr Phe Ser  
 35 40 45  
 Cys Lys Ser Pro Met Ser Ser Leu Val Val Glu Ser Val Leu Ala Ser  
 50 55 60  
 Asp Thr Phe Tyr Ser Cys Asn Met Leu Phe Trp Leu Lys Tyr Val Thr  
 65 70 75 80  
 Lys Ile Trp Ser His Thr Asp Ile  
 85

<210> 195  
 <211> 204  
 <212> PRT  
 <213> Homo sapiens

<400> 195

Val Ser Ser Ala Leu Thr Cys Ser Leu Pro Gly Pro Ala His Gln Thr  
 1 5 10 15  
 Cys Ser Cys Leu Lys Ala Leu Pro Trp Glu Tyr Ser Ser Pro Leu Gln  
 20 25 30

Ser Trp Val Leu Gln Ser Trp Val Leu Pro Ile Ile Gln Phe Lys Ile  
 35 40 45  
 Thr Ser Trp Asp Arg Ser Ser Gln Thr Asn Gln Cys Gly Val Pro Phe  
 50 55 60  
 Leu His Arg Arg Cys Ser Thr Ile Thr Ser Leu Cys Cys Ile Leu Leu  
 65 70 75 80  
 Thr His Ser Ser Gln Ile Ile Leu Cys Ile His Phe Val Ser Phe Leu  
 85 90 95  
 His Leu Pro Arg Ala Thr Leu Ser Val His Val Ala Pro Gly Leu Glu  
 100 105 110  
 Cys Tyr Phe His His Ser Thr His Phe Ser Leu Val Asn Cys Asp Ser  
 115 120 125  
 Ser Ala His Phe Arg Thr Leu Ser Ser Asp Leu Arg Ile Arg Gly Ile  
 130 135 140  
 Asp Thr Arg Val Gly Gly Met Tyr Arg Leu Leu Ile Asp Glu Asn Glu  
 145 150 155 160  
 Lys Ile Ala Arg His Cys Ser Thr Val Glu Val Arg His Glu Leu Cys  
 165 170 175  
 Ile Phe Gln Asp Phe Leu His Leu Leu Leu Thr Ala Trp Val Arg Ile  
 180 185 190  
 Glu Arg Leu Thr Thr Glu Thr Thr Ile Leu Gly Arg  
 195 200

<210> 196  
 <211> 190  
 <212> PRT  
 <213> Homo sapiens

<400> 196

Cys Cys Leu Asp Glu Val Gly Arg Asp Ser Tyr Leu Met Leu Pro Leu  
 1 5 10 15  
 Leu Ser Cys Ser Trp Asn Lys Ser Gln Trp Ser Leu Arg Trp Glu Lys  
 20 25 30  
 Leu Asn Asp Ile Cys Ser Leu Cys Ser Cys Gln Pro Cys Pro Leu Glu  
 35 40 45  
 Ala Pro Thr Leu Phe Leu Leu Lys Leu Pro Ser Val Gln Ile Leu Arg  
 50 55 60  
 Ser Leu Ser Met Ile Ser Phe Pro Ile Ile Val Asp Tyr Cys Leu Asn  
 65 70 75 80  
 Leu Gly Thr Ile Phe Gln Cys Met Ile Glu Ser His Leu Gly Lys Ile  
 85 90 95  
 Tyr Ser His Trp Tyr Leu Lys Glu Arg His Ser Tyr Ser Gly Ser Leu  
 100 105 110  
 Val Tyr Ile Gly Asn Trp Phe Gln Asp Pro Leu Arg Ile Gln Lys Ser  
 115 120 125

Lys His Ile Gln Ala Val Pro Lys Leu Ala Leu Trp Asn Ser Pro Val  
130 135 140

Arg Lys Val Gly Leu Pro Tyr Leu Gln Val Leu Tyr Ser Val Ser Thr  
145 150 155 160

Leu Leu Leu Ile Cys Ile Trp Leu Lys Lys Ile Cys Val Met Asp Pro  
165 170 175

Cys Ser Ser Asn Pro Cys Cys Ser Arg Val Asn Cys Ile Ala  
180 185 190

<210> 197

<211> 197

<212> PRT

<213> Homo sapiens

<400> 197

Gln His Ser Glu Ile Pro Ser Leu Lys Arg Ile Thr Leu Leu Trp Cys  
1 5 10 15

Gly His Lys Arg Arg Gln Ile Leu Lys Glu Asp Leu Asn Asn Trp Lys  
20 25 30

Val Tyr Ile Leu Phe Pro Ile Met Ser Phe Ser Val Pro Phe Pro Leu  
35 40 45

Asp Leu Phe Tyr Phe His Phe Ser Ala Val Ile Leu Tyr Leu Phe Ile  
50 55 60

His Cys Glu His Ile Phe Leu Tyr Val Leu Lys Leu Leu Thr Ile Ile  
65 70 75 80

Ala Tyr Arg Phe Leu Leu Lys Lys Ile Trp Ile Phe Leu His Trp  
85 90 95

Leu Cys Phe Leu Leu Asn Met Gly Ile Phe Leu Val Phe Ser Tyr Val  
100 105 110

Glu Phe Ile Ile Phe Thr Met Ile Cys Gly Asp Trp Ile Leu Leu Ser  
115 120 125

Leu Asn Val Leu Leu Ile Trp Pro Phe Leu Phe Ser Phe Phe Phe Ser  
130 135 140

Phe Leu Ser Lys Glu Leu Ile Leu Ala Glu Phe Trp Ser Pro Leu Pro  
145 150 155 160

Ser Pro Pro Leu Ser Ser Phe Leu Phe Leu Ser Phe Leu Ser Lys Gly  
165 170 175

Leu Thr Leu Ala Glu Phe Arg Phe Gln Thr Ile Val Ser Phe Val Val  
180 185 190

Gly Arg Ser Asn Phe  
195

<210> 198

<211> 210

<212> PRT

<213> Homo sapiens

<400> 198

Phe Phe Ser His Phe Leu Asn Tyr Tyr Phe Pro Leu Phe Leu Val His  
 1 5 10 15  
 Phe Leu His Ile Leu Ile Thr Phe Leu Phe Pro Phe Val Tyr Ile Leu  
 20 25 30  
 Trp Ile Phe Ser Leu Trp Leu Pro Trp Arg Leu His Val Thr Val Gln  
 35 40 45  
 Ser Tyr Asn Asn Leu Phe Ile Asn Thr Asn Leu Thr Ser Ile Ala Pro  
 50 55 60  
 Asn Thr Leu Leu Phe Tyr Asn Phe Pro Phe Leu Leu Cys Tyr Val Ile  
 65 70 75 80  
 Ser Val Lys Asn Gln Ser Leu Tyr Met Leu Cys Thr Tyr His Gly Phe  
 85 90 95  
 Ile Ile Ile Phe Val Asn Leu Pro Phe Lys Phe Phe Lys Lys Ser Val  
 100 105 110  
 Val Thr Ser Gln Asn Tyr Ile Lys Leu Leu Val Phe Ile Met Ser Met  
 115 120 125  
 Tyr Leu Pro Leu Pro Glu Ile Phe Ile Phe Ser Tyr Val Phe Lys Leu  
 130 135 140  
 Leu Ser Ile Val Ile Leu Phe Gln Leu Arg Ala Val Leu Thr Leu Ile  
 145 150 155 160  
 Ile Val Glu Asp Cys Ser Leu Leu Ala Cys Leu Pro Gly Gly Ala Phe  
 165 170 175  
 Ile Phe Ala Phe Gln Asp Ser Phe Ala Lys Tyr Arg Ile Leu Ser Gln  
 180 185 190  
 Val Phe Phe Phe Phe Phe His Leu Lys Tyr Ile Ile Ser Val Pro Ser  
 195 200 205  
 Gly Leu  
 210

<210> 199  
 <211> 202  
 <212> PRT  
 <213> Homo sapiens

<400> 199

Leu Ile Ser Lys Met Arg Met Met Leu Ala Leu Pro Leu Ser Gly Cys  
 1 5 10 15  
 Tyr Lys Asn Gln Met Arg Ile Val Leu Trp Lys Met Leu Ala Lys Asp  
 20 25 30  
 Gln Val Leu His Val Cys Lys Ile Ile Phe Gln Glu Tyr Pro Gln Ser  
 35 40 45  
 Phe Trp Ala Gly Ile Ser Tyr Asn Phe Phe Gln Leu Cys Gly Lys Ile  
 50 55 60  
 Leu Tyr Lys Cys Ile Asp Ile Asp Arg Tyr Phe His Ile Ile His Ala  
 65 70 75 80  
 Val Met Ile Glu Lys Cys Thr Leu Asn Val Leu Ser Phe Asn Ser Thr



85 90 95  
 Gly Asn Leu Asp Met His Glu Ser Phe Lys Thr Met Leu Gln Thr Ser  
 100 105 110  
 Val Ser Phe Arg Ile Leu Cys Leu Phe Leu Thr Pro Asn Pro Lys Met  
 115 120 125  
 Thr Lys Trp Glu Asn Met Pro Ala Cys Thr Ser Cys Leu Gly Arg Tyr  
 130 135 140  
 Ile Lys Gln Trp Val Glu Asp Trp Ile Lys Glu Arg Gln Lys Ala Phe  
 145 150 155 160  
 Thr Gln Val Ile Leu Pro Lys Ile Glu Arg Leu Pro Ala Asn Lys Ile  
 165 170 175  
 Gly Arg Ser Leu Pro Ser Ala Ile Gln Arg Asp Ile Gly Asn Lys Gln  
 180 185 190  
 Leu Tyr Val Cys Val Val Cys Val Cys Val  
 195 200  
 <210> 200  
 <211> 211  
 <212> PRT  
 <213> Homo sapiens  
 <400> 200  
 Ile Leu Tyr Gly Phe Phe Ala His His Asn Pro Arg Ala Arg His Lys  
 1 5 10 15  
 Leu Met Asn Leu Ser Leu Leu Ser Pro Leu Cys Ile Leu Pro Pro Ile  
 20 25 30  
 Ile Leu Thr Pro Ser Ser Pro Leu Asp Phe Tyr Cys Ser Val His Ile  
 35 40 45  
 Lys Ile Phe Leu Gly Ser Lys Thr Gln Leu His Pro Thr Leu Cys Arg  
 50 55 60  
 Tyr Leu Ser Met Phe Phe Ser Leu Phe Pro Thr Ala Asn Phe Ile Leu  
 65 70 75 80  
 His Ile Asp Leu Thr Phe Phe Pro His Ser Leu Thr Lys Leu His Asp  
 85 90 95  
 Ser Gln Pro Gln Thr Ser Pro Asn Tyr Tyr Ile Arg Pro Pro Ser Leu  
 100 105 110  
 Ser Phe Asn Cys Leu Cys Val Ser Leu Pro Thr Arg Ile Ile Pro Ser  
 115 120 125  
 Ile Lys Ile Ser Val Asn Cys His Phe Phe Gln Val Thr Phe Leu Phe  
 130 135 140  
 Leu Phe Tyr Leu Lys Met Gln Phe Phe His Ser Ala Ser Leu Ala Leu  
 145 150 155 160  
 Gln Pro His Leu Phe Tyr Gly Met His Tyr Ile Glu Phe Val Ile Leu  
 165 170 175  
 Leu Gln Ile Leu Thr Ser Ala Gln Ile Leu Phe Glu Val Thr Asn Ser  
 180 185 190

Ala Ser Ile Tyr Leu Cys Val Asn Gly Ile Leu Leu Glu Ser Arg Cys  
 195 200 205

Arg Leu Gly  
 210

<210> 201  
 <211> 132  
 <212> PRT  
 <213> Homo sapiens

<400> 201

Thr Ser Pro Ser Pro Asn Gln Leu Arg Ser Cys Ser Leu Pro Gln Gln  
 1 5 10 15

Ala'Gln Arg Gln Val Leu Leu Pro Phe Pro Thr Glu Arg Arg Leu Leu  
 20 25 30

Phe Cys Thr Ala Pro Arg Ser Leu Asn Ser Leu Pro Gln Pro Val His  
 35 40 45

Cys Pro Gln Arg Cys Pro Thr Val Ser Val Cys Val Gly Val Pro Gly  
 50 55 60

Thr Ala Pro Ser Pro Ser Leu Gly Arg Leu Gly Arg Ala Trp Gly Pro  
 65 70 75 80

Pro Gly Asp Thr Cys Gly Arg Pro Glu Arg Trp Leu Tyr Leu Gly Asp  
 85 90 95

Gly Leu Val Glu Asp Arg Pro His Gln Pro Ala Arg Arg Gly Ser Gly  
 100 105 110

Val Leu Phe Trp Gly Gly Lys Ser Arg Leu His Asp Ile Leu Gly Val  
 115 120 125

Ser Arg Pro Thr  
 130

<210> 202  
 <211> 208  
 <212> PRT  
 <213> Homo sapiens

<400> 202

Thr Asn Leu Asn Tyr Phe Arg Ala Met Asn Lys Ile Asn Ser Ile Thr  
 1 5 10 15

Phe Ile Leu Cys Pro Gln Phe Phe Gln Val Asn Tyr Leu Leu Ala Phe  
 20 25 30

Asp Tyr Tyr Phe Val Ser His Lys Ile Cys Tyr Glu Ser Met Tyr Arg  
 35 40 45

Ile Leu Ser Asp Trp Leu Cys Tyr Cys Asn Gln Arg Cys Val Asp His  
 50 55 60

Pro Val Gln Cys Trp Gln Asp Ile Pro Tyr Ile Met Asn Phe His Ser  
 65 70 75 80

Pro Leu Leu Ala Val Cys Gly Leu Thr Asn Lys Tyr Ser Ile Leu Ile  
 85 90 95

Leu Gln Ala Ile Arg His Phe Ala Glu Cys His Leu Ser Ile Leu Ser  
 100 105 110  
 Lys Ile Leu Phe Phe Leu Glu Ser Asp His Lys Phe Arg Lys Ile Thr  
 115 120 125  
 Lys Met Lys Leu Ile Val Phe Val Leu Pro Lys Leu Cys Leu Ser Cys  
 130 135 140  
 Leu Leu Lys Gln Ile Thr Glu Lys Asn Glu Ala Tyr Ile Lys Lys Phe  
 145 150 155 160  
 Gln Asn Gln Ile Cys Pro Arg Lys Val Thr Leu Phe Leu Ser Ile Ile  
 165 170 175  
 Leu Lys Ile Gln Ser Ile Ser Ser Lys Leu Ile Leu Ile Asp Val Phe  
 180 185 190  
 Lys Leu Leu Arg Leu Asn Asn Tyr Ile Gln Leu Ser Glu Leu Asp Ser  
 195 200 205

<210> 203  
 <211> 94  
 <212> PRT  
 <213> Homo sapiens

<400> 203

Glu Pro Gly Val Leu Asp His Leu Cys His His Thr Val His Pro Leu  
 1 5 10 15  
 Cys Thr Asn Pro Tyr Tyr Pro Lys Thr Lys Lys His Leu Leu Phe Phe  
 20 25 30  
 Ser Ser Cys Asn Leu Phe Ser Asn Lys Leu Ile Leu Gln Ala Gly His  
 35 40 45  
 Leu Ser Asp Ile Ser Arg Ile Cys Ile Ile Phe Leu Tyr Leu Tyr Asn  
 50 55 60  
 Lys Ile Leu Ala Ser Gly Phe Ser Arg Gln Cys Tyr Leu His Tyr Phe  
 65 70 75 80  
 Thr Ile Cys Val Tyr Cys Glu His Tyr Cys Ile Leu Ser Tyr  
 85 90

<210> 204  
 <211> 157  
 <212> PRT  
 <213> Homo sapiens

<400> 204

Ser Ala Lys Ser Ser Leu Thr Ser Leu Ala Leu Ser Val Leu Gly Lys  
 1 5 10 15  
 Leu Ala Asn Ser Asn Arg Trp Gln Leu Arg Leu Val Phe Pro Ala Met  
 20 25 30  
 Val Ile Leu Arg Leu Ser Val Ile Leu Leu Thr Ala Cys Leu Ile Lys  
 35 40 45  
 Met Pro Glu Ser Tyr Val His Val Ser Arg Val Ser Leu Lys Gly Asn  
 50 55 60

Gly Ser Leu Ser Thr Gly Ala Cys Gln Ser Phe Pro Ser His Ala Met  
 65 70 75 80  
 Phe Asp His Val Thr Leu Ser Phe Ile Val Arg Gly Glu Pro Arg Thr  
 85 90 95  
 Ser Leu Trp Ser Leu Lys Glu Met Arg Ala Gln Val Ile Leu Lys Arg  
 100 105 110  
 Ser Tyr Phe Ser Lys Gly Lys Ser Leu Leu Phe Ala His Ser Ser His  
 115 120 125  
 Leu Met Ile Leu Lys Tyr Phe Val Leu Asp Ser Phe Arg Asn Phe Val  
 130 135 140  
 Thr Val Gly Glu Ile Ala Thr Tyr Val Ser Ser Val Leu  
 145 150 155

<210> 205  
 <211> 209  
 <212> PRT  
 <213> Homo sapiens

<400> 205

Pro Leu Leu Ser Trp Val Arg Ile Ala Phe Glu Ile Arg Ile His Leu  
 1 5 10 15  
 Phe Leu Leu Pro Leu Leu Ile Pro Ser Phe Cys Tyr Ser Val Ile Val  
 20 25 30  
 Tyr Phe Leu Ser Lys Thr Leu Gly Arg Ala Leu Gln Leu Leu Asn  
 35 40 45  
 His Glu Thr Ser Phe Asn Leu Ser Ser Val Gln Ile Gln Phe Leu Lys  
 50 55 60  
 Ile Glu Met Phe Leu Pro Thr Tyr His Phe Tyr Phe Leu Cys Val Val  
 65 70 75 80  
 Lys Ile Lys Arg Leu Asp Lys Phe Asp Ile Thr Val Met Ile Thr Gly  
 85 90 95  
 Lys His Lys Gly Ile Asn Phe Ala Phe Ser Leu Glu Asn Pro Ser Val  
 100 105 110  
 Phe Phe Thr Ile Val Arg Arg Asn Tyr Thr Asp Leu Arg Arg Glu Ala  
 115 120 125  
 Asn Glu Asn Phe Leu Ala His Thr Trp Ala Ser Phe Lys Leu Phe Tyr  
 130 135 140  
 Phe Leu Ser Tyr Ile Ile Glu Ser Tyr Gln Lys Ile Phe Met His Ile  
 145 150 155 160  
 Gln Leu Lys Tyr Lys Tyr Lys Tyr Met Tyr Val Cys Val Ser Thr Thr  
 165 170 175  
 Tyr Ile Tyr Ser Asn Asn Lys Arg Lys Phe Val Pro Val Ile Lys Cys  
 180 185 190  
 Ser Ser Gln Ile Cys His Thr Val Lys Gly Leu Leu Cys Ser Leu Asn  
 195 200 205

His

<210> 206  
 <211> 170  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 206

Val Leu Asn Leu Phe Tyr Tyr Trp Leu Leu Val Phe Tyr Cys Asp Val  
 1 5 10 15  
 Ser Leu His Thr Leu His Phe Phe Cys Asn Thr Phe Gly Leu Phe Leu  
 20 25 30  
 Ile Asp Leu Phe Leu Asn Gly Ser Arg Phe Tyr Leu Leu Tyr Ala Leu  
 35 40 45  
 Ile Gly Phe Ser His Cys Cys Leu Pro Phe Asn Leu Ile Leu Trp Ile  
 50 55 60  
 Phe Leu Ser Ile Arg Lys Pro Phe Ala Val Lys Cys Leu Ile Leu Pro  
 65 70 75 80  
 Phe Gly Phe Cys Cys Glu Gln Thr Ser His Leu Lys Val Leu Ser Leu  
 85 90 95  
 Ser Val Ile His Ile Cys Leu Tyr Phe Leu Leu Gly Leu Phe Phe His  
 100 105 110  
 Phe Lys Thr Leu Phe Asp Leu Gly Leu Leu Phe Val Cys Gly Glu Arg  
 115 120 125  
 Gln Asp Pro Asp Leu Ile Leu Phe Gln Gly Val Ser Cys Leu Ser Gln  
 130 135 140  
 Asp His Phe Leu Asn Ser Pro Asp Pro Leu Leu Asp Ser His Leu Ala  
 145 150 155 160  
 Tyr Leu Ile Cys Thr Leu Pro Ala Asn Ile  
 165 170

<210> 207  
 <211> 196  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 207

Leu Asn Tyr Asn Arg Gly Leu Thr His Asp Glu Ser Thr His His Lys  
 1 5 10 15  
 Ala Phe Ser Gln Ile Ala Cys Phe Leu Val Phe Ile Val Gly Tyr Phe  
 20 25 30  
 Val Phe Tyr Tyr Arg Pro Gln Cys Val Leu Lys Cys Pro Phe Val Asp  
 35 40 45  
 Ser Thr Lys Arg Gly Phe Pro Thr Cys Cys Val Lys Thr Lys Phe Leu  
 50 55 60  
 Cys Glu Ile Asn Pro Cys Ile Thr Lys Cys Phe His Arg Tyr Phe Ser  
 65 70 75 80

Asn Phe Asn Pro Gly Val Phe Ser Phe Ser Leu Ala Thr Met Gly Ser  
                     85                    90                    95  
 Glu Thr Ser Phe Cys Arg Phe Tyr Thr Lys Arg Phe Ala Ala Glu Ser  
                     100                    105                    110  
 Lys Lys Arg Arg Asn Ile Arg Ile Asp Thr Ser Gln Ser Ile Phe Thr  
                     115                    120                    125  
 Glu Ser Leu Phe Leu Val Phe Ile Thr Gly Tyr Val Phe Arg Tyr Arg  
                     130                    135                    140  
 Pro Cys Thr Pro Lys Cys Pro Phe Val Asp Ser Thr Lys Arg Val Phe  
                     145                    150                    155                    160  
 Leu Ala Cys Val Lys Glu Lys Val Val Cys Glu Met Asn Thr Arg Ile  
                     165                    170                    175  
 Thr Lys His Phe Tyr Thr Glu Leu Val Pro Ser Phe Tyr Arg Gly Ile  
                     180                    185                    190  
 Phe Cys Phe Ser  
                     195

<210> 208  
 <211> 165  
 <212> PRT  
 <213> Homo sapiens

<400> 208

Ile Gly Ser Gly Ser Phe Cys Val Asn Ser Val Leu Arg Leu Val Phe  
 1                    5                    10                    15  
 Phe His Lys Met Cys Thr Ser Ser Asp Leu Gly Ser Ile Leu Ser Cys  
                     20                    25                    30  
 Ser Tyr Leu Ala Asp Lys Lys Thr Glu Asp Gln Arg Lys Lys His Arg  
                     35                    40                    45  
 Glu Ser Leu Pro Ser Gln Asn Arg Ser Ser Ser Gly Thr Ser Val Ser  
                     50                    55                    60  
 Leu Ala Glu Glu Pro Thr Lys Ser Leu Pro Ser Thr Ile Lys Thr Asn  
                     65                    70                    75                    80  
 Leu Pro Lys Arg Trp Tyr Tyr Gln Pro Ser Met Gly Ser Ala Ser Met  
                     85                    90                    95  
 Asp Ser Thr Asn Gln Gly Ser Lys Ile Phe Arg Lys Arg Ser Val Ser  
                     100                    105                    110  
 Ile Leu Asn Met Tyr Arg Leu Phe Phe Phe Phe Leu Ile Pro Glu Thr  
                     115                    120                    125  
 Ile Gln Tyr Asn Asn Tyr Leu His Asn Ile Tyr Ile Val Leu Gly Val  
                     130                    135                    140  
 Val Ser Asn Leu Glu Val Ile Ser Val Gln Met Phe Gly Gly Tyr Ile  
                     145                    150                    155                    160  
 Gln Ile Leu Cys His  
                     165

<210> 209

<211> 159  
 <212> PRT  
 <213> Homo sapiens

<400> 209

Ala Asn Thr Pro Lys Met Ser Pro Pro Ile Ser Phe Pro Asp Val Ser  
 1 5 10 15  
 Thr Pro Asn His Cys Ser Ser Leu Tyr Cys Phe Leu Ala Gln His Leu  
 20 25 30  
 Thr Leu Phe Val Asp Ile Ile Asn Ile Cys Asn Tyr Phe Pro Tyr Leu  
 35 40 45  
 Phe Thr Gly Phe Glu Phe Asp Ser Leu Pro Leu Val Asn Cys Phe Ser  
 50 55 60  
 Val Ser Val Leu Phe Ser Ile Ile Ser Pro Ala His Gly Leu Val Ser  
 65 70 75 80  
 Ser Thr Tyr Thr Ser Ile Asn Ile Cys Cys Met Asn Ile Cys Asp Gly  
 85 90 95  
 Val Glu Thr Lys Ser Leu Phe Ser Phe Met His Leu Ser Val Cys Ile  
 100 105 110  
 Met Cys Thr Asp Ser Tyr Ile Glu Ile Met Thr Ala Glu Leu Met Glu  
 115 120 125  
 Gly Val Glu Glu Gly Pro Gly Gly Gln Glu Leu Leu Ser Leu His Arg  
 130 135 140  
 Cys Glu Ala Asn Pro Ala Pro Thr Cys Lys Asn Leu Val Leu Thr  
 145 150 155

<210> 210  
 <211> 152  
 <212> PRT  
 <213> Homo sapiens

<400> 210

Gly Ile His Pro Val Val Arg Ala Gly Val Ser Met Glu Glu His His  
 1 5 10 15  
 Ser His Lys Glu Arg Gly Asp Pro Thr Pro Arg Ala Arg Ser Arg Ala  
 20 25 30  
 Leu Arg Gly His Trp Val His Gln Ala Leu Pro Ala Ser Phe Cys Ser  
 35 40 45  
 Pro Asn Ser Gln Gly Pro Pro Val Leu Ser Thr Trp Leu Pro Cys Trp  
 50 55 60  
 Ser Glu Lys Ser Ser Ser Gly Ser Ala Leu Pro Pro Val Asn Ile Arg  
 65 70 75 80  
 Pro Gly Leu Asn Leu Thr Thr His Ile Gly Val Leu His Pro Val Leu  
 85 90 95  
 Asn Phe Pro His Tyr Met Val Thr Ile Pro Arg His Phe Ser Ser His  
 100 105 110  
 Leu Cys His Val His Trp Gly Ser Gly Asp Thr Ser Thr Cys Trp Val

115                      120                      125  
 Glu Gln Lys Gln Asn Gly Phe Ile Arg Phe Cys His Trp Thr Pro Leu  
     130                      135                      140  
 Ala Glu Ser Val Gly Arg Pro Arg  
     145                      150  
 <210> 211  
 <211> 166  
 <212> PRT  
 <213> Homo sapiens  
 <400> 211  
 Phe Pro Ser Ser Arg Cys Ala Asp Ser Pro Arg Ser Leu Ser Ala Pro  
     1                      5                      10                      15  
 Arg Arg Asn Ala Cys Pro Arg Lys Gly Gly Gly Arg Glu Arg Gly Glu  
                     20                      25                      30  
 Glu Gly Glu Ser Arg Ser Gly Gly Glu Gly Gly Arg Arg Ala Arg Trp  
     35                      40                      45  
 Ser Ala Glu Lys Ala Glu Lys Arg Asp Glu Gly Glu Arg Ala Glu Gly  
     50                      55                      60  
 Lys Asp Arg Arg Glu Arg Gly Arg Glu Phe Leu Gly Pro Gly Pro Phe  
     65                      70                      75                      80  
 Thr Arg Ser Val Trp Gln Val Pro Arg Arg Pro Arg Thr Gly Leu Ala  
                     85                      90                      95  
 Lys Pro His Arg Leu Leu Pro Gly Trp Leu Pro Asp Gln Gly His Ala  
                     100                      105                      110  
 Glu Val Gly Ala Cys Pro Glu Ala Thr Pro Gly Gln Ala Glu Lys Glu  
     115                      120                      125  
 Gly Thr Arg Asp Phe His Ala Ser Gly Asn Ile Thr Val Gly Trp Ala  
     130                      135                      140  
 Thr Ser Ala Ala Ile Ile Arg Glu Ser Pro Leu Pro Gln Ala Trp Pro  
     145                      150                      155                      160  
 Leu Pro Arg Ser Ile Ile  
                     165  
 <210> 212  
 <211> 225  
 <212> PRT  
 <213> Homo sapiens  
 <400> 212  
 Lys Tyr Arg Asp Thr Arg Asn Leu Asn Pro Gly Thr His Cys Gln His  
     1                      5                      10                      15  
 Ile Ser Asn Gly Arg Gln Gly Val Ile Glu Thr Lys Gly Trp Lys Ala  
                     20                      25                      30  
 Leu Phe Phe Cys Pro Trp Val Phe Thr Asp Trp Phe Cys Pro Glu Gln  
     35                      40                      45  
 Val Leu Ser Thr Lys Ile Phe Val Ala Ile His Gly Lys Ile Gln Gln



50                      55                      60  
 Leu Cys Tyr Asp Cys Cys Tyr Leu Leu Tyr Cys Tyr Cys Phe Ile Ser  
 65                      70                      75                      80  
 Ser Leu Ile Asp Leu Lys Ile Leu His Leu Met Val Lys Leu Asp Phe  
                     85                      90                      95  
 Leu Phe Cys Gln Phe Tyr Leu Asn Asn Leu Leu His Tyr Ile Gln Gly  
                     100                      105                      110  
 Lys Ile His Ser Lys Ile Asn Arg Arg Arg Glu Gly Tyr Ala Gln Ser  
                     115                      120                      125  
 Ser Ser Val Lys Leu Ser Thr Pro Lys Val Thr Val Gly Ala Ser Gln  
                     130                      135                      140  
 Asp Phe Phe Lys Asn Gln Lys His Cys Leu Cys Ser Lys His Leu Thr  
 145                      150                      155                      160  
 Ser Ser Glu Leu Ala Tyr Lys Val His His Met Gln Glu Ser Leu Leu  
                     165                      170                      175  
 His Ile Lys Phe Ile Ile Met Ile Trp Phe Ile Phe Gly Tyr Ser Asp  
                     180                      185                      190  
 Arg Tyr Ser Phe Phe Ile Asn Pro Val Gly Arg Pro Lys Ser Ile Ser  
                     195                      200                      205  
 Val Val Leu Gln Cys Leu Tyr Cys Leu Ser Pro Ile Phe Leu Cys Thr  
                     210                      215                      220

Phe  
225

<210> 213  
 <211> 195  
 <212> PRT  
 <213> Homo sapiens

<400> 213

Tyr Pro Ala Leu Ser Val Tyr Asp Ala Ile Ser Val Leu Cys Ser Asp  
 1                      5                      10                      15  
 Leu Ser Asp Cys Arg Lys Arg Ile Asn Phe Phe Asn Ala Val Glu Thr  
                     20                      25                      30  
 Leu Asn Arg Tyr Arg Gln Ser Ile Phe Thr Phe Ser Tyr Ile Ser Ile  
                     35                      40                      45  
 Ile Leu Lys Met Arg Thr Phe Gln Lys Ser Ile Ile Gln Val Tyr Ser  
                     50                      55                      60  
 Lys Met Cys Arg Asn Asn Ser Cys Phe Thr Gly Asp Ser Pro Lys Asp  
 65                      70                      75                      80  
 Met Cys Leu Glu Val Leu Val Ser Ile Arg Phe Ser Ser Gln Ala Lys  
                     85                      90                      95  
 Asp Ser Leu Glu Pro Met His Leu Trp Leu Ile Phe Trp Asp Lys Asn  
                     100                      105                      110  
 Lys Ala Arg Asn Gly Glu Ala Tyr Ser Ile Ser Leu Lys Ile Ser Ala  
                     115                      120                      125

Phe Lys Ile Lys Thr Leu Leu Lys Leu His Ile Leu Phe Ser Cys Ile  
 130 135 140  
 Cys Phe Tyr Cys Phe Val Asn Tyr Asn Ser Ser Ile Lys Arg Asn Arg  
 145 150 155 160  
 Thr Tyr Ala Ile Leu Ser Cys Asp Ser Pro Arg Thr Phe Ser Lys Leu  
 165 170 175  
 Phe Tyr Leu Ile Ala Leu Ser Leu Ile Met Gly Ile Ser Ser Leu Asn  
 180 185 190  
 Cys Cys Ser  
 195

<210> 214  
 <211> 133  
 <212> PRT  
 <213> Homo sapiens

<400> 214

Arg Thr Gly Lys Arg Asn Ala Met Thr Leu Ile Asn Ile Lys Leu Glu  
 1 5 10 15  
 Phe Cys Ser Gly Gln Asn Thr Ser Arg Gln Gly Ser Ile Thr His Ser  
 20 25 30  
 Val Ser Thr Ser Phe Phe Ile Ser Leu Phe Ile Ser His Met Cys Leu  
 35 40 45  
 Ser Gly Ile Pro Ser His Asn Leu Val Thr Tyr Leu Ile Thr Arg Leu  
 50 55 60  
 Ser Thr Gln Cys Phe Ala His Arg Lys Cys Ser Val Tyr Ala Ser Ser  
 65 70 75 80  
 Pro Gly Cys Leu Cys Arg Val Val Tyr Tyr Gln Asn Ala Leu Tyr Ser  
 85 90 95  
 Leu Phe Lys Ala Ser Leu Tyr His Val Gly Met Ile Leu Lys Thr Val  
 100 105 110  
 Asn Val Lys Cys Leu Thr Tyr Ser Ser Asp Pro Leu Leu Arg Asn Val  
 115 120 125  
 Leu Arg Arg Thr Val  
 130

<210> 215  
 <211> 219  
 <212> PRT  
 <213> Homo sapiens

<400> 215

His Asn Cys Gly Lys Asp Leu Ser Gln Gly Pro Gly Tyr Gln Tyr Ala  
 1 5 10 15  
 Ser Cys Tyr Leu Gly Met Met Tyr Phe Lys Lys Phe Ile Val Ile Ile  
 20 25 30  
 Glu Asn Trp Leu Phe Ile Pro Asn Ile Leu Asn Phe Leu Phe Ile Gly  
 35 40 45

Ser Phe Asn Lys Met Tyr Tyr Ile Leu Ser Leu Asn Leu Val Arg Pro  
 50 55 60  
 Lys Ile Val Glu Pro Phe Phe Val Phe Ala Phe Asp Asp Pro Gly Ser  
 65 70 75 80  
 Leu Thr Leu Ile Ser Ile Leu Tyr His Asn Lys Asn Ile Gln Asn Tyr  
 85 90 95  
 Cys Cys Ile Thr Ile Pro Ser Ser Ser Ala Val Leu Cys Tyr Leu Ser  
 100 105 110  
 Phe Thr Ala Val Met Pro Leu Ser Ala Phe Tyr Ser Phe Leu Arg Pro  
 115 120 125  
 Pro Asn Phe Pro Leu Pro Val Cys Leu Tyr Leu Gly Asp Gln Ser Ser  
 130 135 140  
 Asn Leu Leu Cys Leu Lys Glu Gln Leu Gly Phe Glu Gly Pro Ser Ser  
 145 150 155 160  
 Leu Phe Cys Glu Ser Val Gly Thr Leu Val Tyr Gly Leu Gln His Val  
 165 170 175  
 Phe Gln Leu Leu Asn Ser Phe Cys Leu Gly Leu Thr Gly Leu Cys Ser  
 180 185 190  
 Tyr Leu Met Ser Pro Asp Asn Leu Pro Asp Lys Ser Val Thr Gly Leu  
 195 200 205  
 Glu Phe Cys Leu Cys Arg Leu Pro Val His Cys  
 210 215

<210> 216  
 <211> 211  
 <212> PRT  
 <213> Homo sapiens

<400> 216

Asn Leu Tyr Pro Arg Arg Lys Ala Asp Arg Trp Ile Asp Met Asn Asn  
 1 5 10 15  
 Val Ile Ser Leu Phe Ala Ser Glu Lys Leu Glu Thr Gly Glu Lys Met  
 20 25 30  
 Gln Ser Val Tyr Pro Thr Pro Gln Arg Gly Arg Val Ile Phe Trp Leu  
 35 40 45  
 Leu Lys Tyr Cys Gln Lys Met Tyr Leu Leu Phe Ile Thr Tyr Ser Ser  
 50 55 60  
 Ile Ser Phe Val Asn Trp Leu Ile Pro Lys Asn Leu Leu Glu Phe Asn  
 65 70 75 80  
 Gly Ser Ser Cys Asp His Thr Gln Gly Ile Thr Ile Ile Tyr Thr Phe  
 85 90 95  
 Ile Gly Tyr Cys Ser Ala Asn Ile Asn Asn Ile Val Thr Arg Asp Leu  
 100 105 110  
 Gln Gln Glu Lys Arg Lys Arg Phe Phe Lys Cys Ser Lys Gly Lys Lys  
 115 120 125

Arg Glu Lys Ile Leu Met Thr Lys Ser Ile His Pro Arg Glu Lys Thr  
 130 135 140  
 Asn Asp Lys Thr Glu Arg Gly Arg Glu Gly Ala Thr Leu Arg Glu Gly  
 145 150 155 160  
 Leu Met Gly Asp Glu Arg Tyr Leu Trp Gly Ser Ser Leu Phe Trp Ala  
 165 170 175  
 His Tyr Cys Leu Ser Pro Val Ala Pro Gln Arg Leu Pro Pro Gly Leu  
 180 185 190  
 Cys Ser Gln Met His Val Tyr Ser Pro Cys Thr Gln Leu Ser Glu Thr  
 195 200 205  
 Ser Ser Val  
 210

<210> 217  
 <211> 187  
 <212> PRT  
 <213> Homo sapiens

<400> 217

Ser Ser Phe Val Ser Phe Ser Phe Trp Trp Leu Leu Ala Ile Leu Gly  
 1 5 10 15  
 Val Pro Trp Leu Val Asp Thr Ser Pro Gln Ser Leu Leu Leu Ser Ser  
 20 25 30  
 His Gly His Leu Pro Tyr Val Ser Val Phe Phe Pro Val Ser Tyr Lys  
 35 40 45  
 Thr Ser Val Ile Arg Phe Lys Ala His Pro Ile His Asp Asp Leu Ile  
 50 55 60  
 Ser Arg Ser Leu Ser Leu Cys Leu Gln Ser Ser Phe Ser Lys Gly His  
 65 70 75 80  
 Asn Leu Lys Phe Val Asn Val Ser Leu Gly Ala Arg Arg Met Leu Phe  
 85 90 95  
 Asn Leu Leu Lys Thr Thr Tyr Leu Val Phe Arg Ile Leu Lys His Ala  
 100 105 110  
 Ser Val Cys Met Tyr Ile Val Arg Trp Ile Tyr Arg Ser Tyr Tyr Leu  
 115 120 125  
 Val Leu Thr Lys Leu Ile Phe Thr Lys Tyr Thr Ser Gly Ser Lys Asn  
 130 135 140  
 Phe Arg Gln Lys His Pro Thr Tyr Thr Gln Gln Ser His Lys Pro Lys  
 145 150 155 160  
 Arg Ile Gly Lys Leu Lys Gly Leu Leu Ser His Pro Leu Tyr Lys Leu  
 165 170 175  
 Phe Val Ser His Lys Leu Pro His Asn His Thr  
 180 185

<210> 218  
 <211> 206  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 218

Thr Ser Asn His Ser Val Ile Arg Leu Ile Leu Tyr Leu Thr Ser Ser  
 1 5 10 15  
 His Gln Asn Tyr Phe Ser Asn Cys Arg Thr Asn His Val Ser Leu Lys  
 20 25 30  
 Phe Leu Ile Arg Ala Asp Leu Ser Val Gly Leu Gln Thr Leu Thr Val  
 35 40 45  
 Arg Pro Gln His Thr Phe Pro Ala Leu Ser Ser Leu His Thr Val Leu  
 50 55 60  
 Trp His Glu Ser Thr Ile Ala His Gly Ser Ile Thr Cys Ser Leu His  
 65 70 75 80  
 Thr Met Gln Leu Cys Ser Phe Cys Phe Glu Gly Phe Pro Pro Ala Leu  
 85 90 95  
 Leu Asp Arg Ser Glu Pro Thr Leu His Gly Pro Ala His Arg Pro Thr  
 100 105 110  
 Pro Leu Asn Leu Phe Phe Leu Leu Pro Ile His Gly Gly Leu Ile Cys  
 115 120 125  
 Cys Glu Ser Lys Arg Thr Ser His Cys Cys Cys Asn Pro Tyr Ser Leu  
 130 135 140  
 Glu Phe Tyr Glu Asn Tyr Val Asn Ser Glu Leu Leu Lys Val Leu Ala  
 145 150 155 160  
 Arg Gly Ser Gly Ser Leu Tyr Phe Cys Ile Leu Ile Ser Pro Ser Pro  
 165 170 175  
 His Ser Asp Leu Leu Phe Asn Asp Tyr Pro Ser Met Ser Pro Ser Arg  
 180 185 190  
 Asn Ser Ile Arg Ser Phe Pro Lys Tyr Gln Pro Asn Thr Thr  
 195 200 205

&lt;210&gt; 219

&lt;211&gt; 249

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 219

Trp Leu Cys Val Ser Val Gln Lys Arg Leu Arg Gly Arg His Gly Ala  
 1 5 10 15  
 Thr Val Gln Glu Ser Leu Gly Leu Leu Thr Ala Thr Ser Gln Pro Leu  
 20 25 30  
 Pro Gly Arg Thr Pro Arg Ser Gly Cys Gln Gly Arg Gly Gly Pro Trp  
 35 40 45  
 Pro Gly Ser Leu Gly Pro Gly Glu Leu Pro Val Leu Pro Ala Gln Ser  
 50 55 60  
 Pro Pro Gly Cys Cys Arg Leu Leu Ala Thr Pro Thr Ser Gln Ala Trp  
 65 70 75 80  
 Arg Glu Ala His Ser Cys Cys Cys Thr Thr Leu Val Asn Val Trp Gly

85 90 95  
 Glu Ala Trp Ala Trp Pro Ala Pro Leu Pro Gly Leu Gln Thr Pro Ala  
 100 105 110  
 Gln Pro Gln Tyr Leu Lys Glu Pro Gln Trp Ser Gln Ala Arg Asp Val  
 115 120 125  
 Glu Asn Ser Gly Phe Gln Glu Thr Leu Ala Leu Leu Leu Ala Ala Pro  
 130 135 140  
 Gly Gly Phe Gln Leu  
 145

<210> 220  
 <211> 101  
 <212> PRT  
 <213> Homo sapiens

<400> 220

Leu Ala Gly Phe Pro Ser Pro Gly Gly Cys Ser Ala Asp Ser Leu Ser  
 1 5 10 15  
 Gly Trp Leu Arg Leu Gln Pro Ala Ala Ile Val Cys Leu Pro Glu Lys  
 20 25 30  
 Ser Ile Ala Asp Glu Pro Gly Ala Leu Gly Glu Arg Glu His Thr Glu  
 35 40 45  
 Ser Phe Leu Thr Ile Ser Pro Ala Glu Ser Tyr Ile Gly Ala Ala Thr  
 50 55 60  
 Pro Tyr Leu Val Leu Ser His Cys Leu Ser Glu Gly Val Leu Gly Leu  
 65 70 75 80  
 Pro Gln Ala His Ser Lys Met Ser Pro Val Ala Lys Ala Leu Gly Pro  
 85 90 95  
 Asp Ser Arg Pro Phe  
 100

<210> 221  
 <211> 215  
 <212> PRT  
 <213> Homo sapiens

<400> 221

Thr Trp Thr His Ser Cys Asp Tyr Ile Gln Pro Leu Gly Trp Leu Lys  
 1 5 10 15  
 Trp Arg Arg Pro Arg Ile Ala Pro Leu Thr Cys Leu Ala Val Ala Ser  
 20 25 30  
 Gly Trp Gly Lys Gly Thr Leu Ile Leu Leu His Arg Val Ser His Pro  
 35 40 45  
 Leu Val Glu Thr Ile Phe Leu Ala Trp Leu Ser Gln Gly Ser Ile Pro  
 50 55 60  
 Arg Met Trp Lys Gly Asn Leu Gln Ser Leu Leu Gln Pro Ser Leu Glu  
 65 70 75 80  
 Ser His Thr Lys Phe Leu Pro Leu His Phe Ile Phe Lys Ala Ser His

85                      90                      95  
 Lys Ala Thr Leu Asp Phe Gly Val Gly Lys Thr Ala Ala Leu Asp Glu  
                     100                      105                      110  
 Asn Thr Ala Trp Val Phe Phe His Cys Cys Ala Cys Gly Cys Ala Phe  
                     115                      120                      125  
 Val Leu Phe Leu Asn Ser Cys Tyr Leu Thr Glu Glu Val Val Ser His  
                     130                      135                      140  
 Lys Asn Lys Gln Val Leu Asn Gln Ser Thr Val Gln Ile Pro Ala Pro  
                     145                      150                      155                      160  
 Pro Ser Ser Thr Thr Thr Tyr Leu Ser Gly Leu Tyr Ile Leu Tyr Leu  
                     165                      170                      175  
 Phe Tyr Lys Val Leu Lys Thr Val Pro Gly Ala Ile Lys Lys Asp Thr  
                     180                      185                      190  
 Gln His Tyr Leu Ser Phe Ser Ser Ile Leu Met Phe Tyr Phe Ser Thr  
                     195                      200                      205  
 Pro Leu Tyr Asn Ile Asn Ile  
                     210                      215

<210> 222  
 <211> 127  
 <212> PRT  
 <213> Homo sapiens

<400> 222

Ser Lys Arg Ile Ile Pro Glu Leu Ser Ser Pro Gln Gly Met Tyr Glu  
 1                      5                      10                      15  
 Asn Pro Arg Glu Trp Ile Asn His Phe Ala Glu Cys Tyr Ala Thr Phe  
                     20                      25                      30  
 Thr Thr Val Ile Ile Pro Gln Cys Lys Lys Asp Leu Leu Lys Met Phe  
                     35                      40                      45  
 Leu Pro Asn Lys Leu Val Phe Ile His Leu Phe Ile Pro Phe Ser Ile  
                     50                      55                      60  
 Asn Leu Leu Ile Ile Ser Val Cys Gln Ala Gln Phe Leu Asp Cys Leu  
                     65                      70                      75                      80  
 Phe Thr Asn Lys Leu Asp Ser Lys Val Cys Tyr His Asn Gly Met Leu  
                     85                      90                      95  
 Phe Pro Trp Gly Lys Thr Arg Thr Met His Lys Gln Val Tyr Asp Thr  
                     100                      105                      110  
 His Ile Ile His Lys Gly Lys Leu Met Asn Trp Met Ser Leu Lys  
                     115                      120                      125

<210> 223  
 <211> 167  
 <212> PRT  
 <213> Homo sapiens

<400> 223

His Val Ser Ser Ser Leu Glu Lys Thr Phe Ile Asn Gly Pro Val Ser

Arg 1	Pro	Gly	Ala	Trp 5	Leu	Ala	Gly	Pro	Cys 10	Cys	Trp	Arg	Cys	Arg 15	Ala
His	Pro	Phe	Val 20	Val	Leu	Gly	Leu	Ala 25	Cys	Gln	Val	His	Cys 30	Gly	Cys
Pro	Pro	Thr 35	Pro	Ser	Trp	Phe	Pro 40	Cys	Gly	Arg	Gly	Ala 45	Val	Arg	Leu
Pro 50	Leu	Cys	His	His	His	Gln 55	Pro	Gly	Phe	Cys	Thr 60	Asp	Phe	His	Ser
His 65	Leu	Phe	Leu	Ala	Cys 70	Phe	Met	Leu	Val	Leu 75	Thr	Gln	Ser	Ser	Ile 80
Phe	Ser	Leu	Leu	Ser 85	Met	Ala	Ile	Asn	Arg 90	Tyr	Leu	Ala	Ser	His 95	Ser
Arg	Leu	Arg	His 100	Lys	Ser	Leu	Val	Thr 105	Gly	Thr	Gln	Thr	Arg 110	Gly	Val
Thr	Ala	Val 115	Leu	Trp	Val	Leu	Ala 120	Phe	Gly	Thr	Gly	Leu 125	Thr	Pro	Phe
Leu	Glu 130	Trp	Asn	Ser	Lys	Asp 135	Ser	Thr	Ser	Asn	Asn 140	Cys	Met	Glu	Pro



Trp Asp Gly Thr Met Asn Glu Ser Cys Cys Leu Val Lys Cys Leu Phe  
 145 150 155 160  
 Gln Asn Ala Val Pro Met Ser Tyr Met Val Tyr Phe Ser Phe Gly Gly  
 165 170 175  
 Val Leu Pro Pro Leu Leu Val Met Trp Leu Ile Ser Ile Lys Phe Phe  
 180 185 190  
 Thr Val Thr Ala Gly Ser Phe Ser Thr Arg Ser Trp Thr Thr Gln Gly  
 195 200 205  
 Pro Pro Ser Ser Gly Arg Tyr Thr Gln Pro Ser Arg Trp Leu Trp Trp  
 210 215 220  
 Gly Met Phe Ala Leu Cys Ser Leu Pro Val Arg  
 225 230 235

<210> 225  
 <211> 209  
 <212> PRT  
 <213> Homo sapiens

<400> 225

Gln Glu Thr Gly His Ala Leu Cys Gln Ala Ala Ser Ser Thr His Ala  
 1 5 10 15  
 Ala Pro Phe Gln His Leu Cys Ser Ser Ile His Ala Leu Lys Ser Leu  
 20 25 30  
 Asn Ser Pro Pro Arg His Gly Leu Pro Ser Arg Ala Gly Met Gly Pro  
 35 40 45  
 Phe Leu Val Ser His Ala Arg Ser Pro Pro Glu Ser Cys Met Asn Asn  
 50 55 60  
 Arg Leu Asp Pro Cys Phe Gln Ser Glu Asp Thr His Glu Ile Phe Pro  
 65 70 75 80  
 Lys Ile Phe Phe Arg Ser Arg His Tyr Cys Glu Tyr His Ile Asn Lys  
 85 90 95  
 Leu Ser Leu Phe Gln Phe Leu Phe Lys Trp Arg Ile Ser Ile Ser Gly  
 100 105 110  
 Ser Asn Leu Thr Cys Lys Lys Asn Asn Arg Phe Phe Lys Lys Phe Gln  
 115 120 125  
 Phe Ile Thr Leu Asn His Ser Tyr Leu Pro Met Leu Gln Cys Thr His  
 130 135 140  
 Lys Lys Leu Val Phe Lys Asp Cys His Leu Cys Leu Leu Gly Lys Thr  
 145 150 155 160  
 Cys Ile Tyr Pro Ser Phe Leu Lys Asn Ser Ile Met Leu Asn Phe Gln  
 165 170 175  
 Ser Asp Ser Val Leu Asp Ser Phe Thr Lys Leu Gln Ser Leu Cys Leu  
 180 185 190  
 Gln Ser Tyr Phe Tyr Val Thr Thr Glu Ala Pro Ser Thr Leu Val Ser  
 195 200 205

Glu

<210> 226  
 <211> 192  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 226

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Leu Cys Leu Thr Lys Val Pro Gly Phe Glu Leu Ala Pro Phe Gly Cys
1          5          10          15
Phe Ser Asp Leu Asn Tyr Tyr Thr His Thr His Ile Met Ser Asn Gly
20          25          30
Gln Asn Glu Gly Phe Trp Asp Ser Gly Ile Pro His His Leu Tyr Tyr
35          40          45
Phe Leu Gly Ser Phe Leu Tyr Gln Asn Met Met Cys Leu Ile Trp Ser
50          55          60
Phe Asn Ser Met Ser Asn Tyr Pro Thr Leu Leu Gln Thr Cys Lys Cys
65          70          75          80
Arg Glu Gln Cys Asn Gly Phe Lys Leu Leu Phe Leu His Gly Lys Phe
85          90          95
Cys Leu Gln Lys Gln Met Gln Arg Lys Asp Gly Val Ser Val Ala His
100         105         110
Cys Leu Trp Asn Ile Cys Arg Asp Ser Arg Arg Ala Ile Ile Lys Ile
115         120         125
Ile Gly Thr Glu Ala Leu Val Leu His Ser Thr Ile Leu Tyr Tyr Tyr
130         135         140
Tyr Gly Ile Cys Met His Ser Val Ser Ala Cys Gln Thr Thr Thr Asn
145         150         155         160
Pro Phe Cys Ile Ile Lys Gln Asn Cys Leu Glu Leu Tyr Phe Met Asn
165         170         175
Gln Phe Glu Ser Tyr Ile Ser Leu Phe Arg Leu Ser Gly Leu Leu Gln
180         185         190

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<210> 227  
 <211> 190  
 <212> PRT  
 <213> Homo sapiens

&lt;400&gt; 227

```

Phe Ser Ala Lys Asp Pro Phe Ile Asn Lys Thr Ala Thr Gly Ser Asn
1          5          10          15
Phe Asn Cys Ile Leu Pro Gly Leu Cys Phe Phe Asn Tyr Phe Phe Ala
20          25          30
Val Val Thr Glu Pro Phe His Val Ser Glu Ile His Thr Phe His Ala
35          40          45
Phe Thr Ile Arg Val Trp Pro Val Met Ala Pro Gln Ile Leu Tyr Thr
50          55          60

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Ile Pro Leu Leu Val His Phe Ile Asn Leu Leu Val Tyr Phe Lys Ser  
 65 70 75 80  
 Val Phe Tyr Leu Arg Lys Lys Arg Asn Phe Ser Val Tyr Lys Asp His  
 85 90 95  
 Ile Val Leu Pro Tyr Thr Ser Thr Phe Val Tyr Ile Val Tyr Cys Cys  
 100 105 110  
 Ile His Thr Ile Val Pro Ser Ser Gln Asp Trp Lys Gln Ser Pro Ala  
 115 120 125  
 Thr Pro Thr Val Trp Glu Gly Cys Gln Thr Lys Leu Trp Asp Thr Ser  
 130 135 140  
 Pro Gln Asn Ser Gly Leu Lys Leu Val Ser Phe Leu Pro Gln Val Pro  
 145 150 155 160  
 Gln Glu Cys Ile Val Thr Val Thr Ala Gly Phe Thr Ser Val Ile Phe  
 165 170 175  
 Lys Cys Leu Cys Glu Phe Pro Lys Ser Thr Gln Ser Ser Ser  
 180 185 190

<210> 228  
 <211> 187  
 <212> PRT  
 <213> Homo sapiens

<400> 228

Arg Thr Ala Thr Val Gly Ser Val Ser Leu Leu Gln Ser Asp Thr Phe  
 1 5 10 15  
 Phe Pro Phe Asp Phe Ser Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr  
 20 25 30  
 Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser  
 35 40 45  
 Phe Glu Asp Leu Leu Ala Asn Asn Ile Leu Arg Ile Phe Val Trp Val  
 50 55 60  
 Ile Ala Phe Ile Thr Cys Phe Gly Asn Leu Phe Val Ile Gly Met Arg  
 65 70 75 80  
 Ser Phe Ile Lys Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile  
 85 90 95  
 Leu Cys Cys Lys Tyr Val Ser Ser Ile Ser Arg Leu Arg Ile Ser Ser  
 100 105 110  
 Val Ser Cys Ala Leu Asp Ile Tyr Met Tyr Leu Leu Ala Phe Asn Lys  
 115 120 125  
 Trp His Leu Met Ile Ile His Pro Gly His Ile Phe Phe Ser Lys Tyr  
 130 135 140  
 Lys Ser Ser Gly Ser Leu Trp Leu Cys Phe Arg Leu Tyr Asp Leu Thr  
 145 150 155 160  
 Val Ala Cys Ser Gln Glu Tyr Val Leu Gly Met Gly Ala Thr Asn Glu  
 165 170 175  
 Ser Ser Asp Arg Leu Ser Phe Val Gly Asp Lys

180

185

<210> 229  
 <211> 210  
 <212> PRT  
 <213> Homo sapiens

<400> 229

Glu Leu Lys Gln Lys Thr Ala Pro Cys Leu His Cys Phe Leu Glu Phe  
 1 5 10 15  
 His Phe His Glu Thr Tyr Gln Glu Gly Pro Gly Arg Trp Gly Ser Arg  
 20 25 30  
 Phe Met Leu Ser Leu Thr Gly Arg Arg Glu Asn Arg Phe Lys Thr His  
 35 40 45  
 Arg Asn Gly Glu Ile Ile Ala Arg Glu Cys Trp Arg Thr Thr Gln Gly  
 50 55 60  
 Ala Gly Ile Leu Arg Cys Ser Leu Val Leu Cys Glu Ser Arg Ile Ala  
 65 70 75 80  
 Gln His Val Gln Met Ser Gly Ala Gly Thr Trp Thr Leu Leu His Val  
 85 90 95  
 Pro Val Leu Phe Pro Thr Tyr Pro Glu Cys Gln Pro Ser Pro Gln Ala  
 100 105 110  
 Met Ala Val Pro Asn Met Lys Phe Arg Val Arg Val Val Ile Gln Ile  
 115 120 125  
 Pro Pro Asn Asn Pro Thr Val Cys Leu Ala Met Ser Ser Phe Leu His  
 130 135 140  
 Ser Ser Tyr Leu Asn Ser Trp Ile Val Thr Leu Tyr His Pro Val Ile  
 145 150 155 160  
 His Arg Trp Val Ser Thr Glu His Thr Ala Met Arg Ile Pro Gly Trp  
 165 170 175  
 His Trp Pro Thr Lys Gln Cys Gln Cys Arg Leu Ala Pro Ala Ser Ser  
 180 185 190  
 Lys Gln Thr Ser Pro Val Leu Arg Asp Thr Ser Met Gln Arg Gly Ile  
 195 200 205  
 Ser Ala  
 210

<210> 230  
 <211> 181  
 <212> PRT  
 <213> Homo sapiens

<400> 230

Gly Ser Thr Leu Leu Ala Glu Tyr Thr His His Lys Leu Val Ser Gln  
 1 5 10 15  
 Gln Ser Phe Cys Leu Val Phe Met Gly Lys Ile Ile Leu Phe His Arg  
 20 25 30  
 Arg His Gln Ser Ala Pro Asn Val His Ile Gln Tyr Thr Thr Glu Arg

35                      40                      45  
 Val Phe Gln Thr Cys Ser Met Lys Gly Asn Leu Gln Leu Tyr Glu Leu  
   50                      55                      60  
 Asn Ala Asp Ile Arg Lys Lys Phe Leu Arg Met Leu Leu Ser Thr Phe  
   65                      70                      75                      80  
 Tyr Leu Asn Ser Arg Phe Gln Arg Asn Pro Pro Ser Tyr Pro Asn Ile  
                           85                      90                      95  
 His Leu Gln Ile Pro Gln Lys Glu Cys Phe Lys Thr Ala Leu Tyr Gln  
   100                      105                      110  
 Trp Gln Ser Ser Thr Leu Leu Val Glu Asp Thr Tyr His Gln Gln Val  
   115                      120                      125  
 Ser Glu Asn Ala Ser Val Tyr Phe Leu Trp Glu Asp Ile Ser Phe Phe  
   130                      135                      140  
 Thr Val Gly Val Lys Ala Ile Glu Met Ser Thr Ser Thr Asn Tyr Lys  
   145                      150                      155                      160  
 Lys Ser Val Ser Asn Leu Leu Tyr Glu Arg Pro Cys Ser Ser Leu Val  
                           165                      170                      175  
 Glu Trp Lys Tyr Pro  
                           180

<210> 231  
 <211> 248  
 <212> PRT  
 <213> Homo sapiens

<400> 231

Cys His His Thr Gln Thr Ser Gln Ala Phe Leu Thr Leu Val Phe Trp  
   1                      5                      10                      15  
 Leu Met Ile Ser Tyr Ala Cys Phe Ile Gly Val Ile Thr Thr Phe Ile  
                           20                      25                      30  
 Ser Glu Glu Ser Asn Ile Leu His Leu Ser Ser Val Gln Ala Leu Leu  
   35                      40                      45  
 Tyr Tyr Leu Lys Cys Phe Lys Asn Phe Ser Tyr Leu Phe Ser Leu Leu  
   50                      55                      60  
 Ala Thr Phe His Tyr Ile Cys Leu Leu Cys Phe Arg Ile Leu Ile Tyr  
   65                      70                      75                      80  
 Arg Leu Ile Phe Ser Arg Arg Glu Gly Glu Gly Lys Arg Glu Arg Glu  
                           85                      90                      95  
 Arg Glu Cys Phe Ser Thr Cys Ser His Val Cys Leu Phe Leu Thr Ala  
   100                      105                      110  
 Phe Thr Gln Ser Ser Arg Leu Ser Gly Ser Lys Gln Gly Leu Tyr Val  
   115                      120                      125  
 Gly Ser Leu Val Phe Gly Ser Ile Ala Asp Pro Val Gln Gly Ala Ala  
   130                      135                      140  
 Ser Ser Ser Leu Tyr Val Val Ser Gly Pro Cys Ala Thr Ser Lys Thr  
   145                      150                      155                      160

Gln Leu Asp Ala Gly Gln Val Thr Pro Glu Thr Ser Gln Leu Pro Val  
 165 170 175  
 Ile Arg Ile Glu Leu Gln Ala Thr Ser Ala Lys Gln Ile Gln Ser Leu  
 180 185 190  
 Asp Pro Arg Val His Arg Leu Ser Ser Thr Tyr Leu Cys Val Phe Glu  
 195 200 205  
 Ile Thr Lys Ala Phe Phe Met Tyr His Ile Trp Val Ile Ile Tyr Ile  
 210 215 220  
 Phe Val Ile Leu Leu Leu Trp Phe Gly Tyr Asp Leu Phe Val Pro Thr  
 225 230 235 240  
 Lys Thr His Val Glu Ile Arg Ser  
 245

<210> 232  
 <211> 163  
 <212> PRT  
 <213> Homo sapiens

<400> 232

Phe Glu Val Arg Gly Ile Leu Leu Phe Asn Phe Leu Ile Ile Lys Leu  
 1 5 10 15  
 Phe Leu Arg Thr Ser Leu Lys Val Asn Asp Trp Thr Trp Asp Gln Ala  
 20 25 30  
 Pro Lys Lys Ile Asn Pro Val Gln Ile Leu Ser Thr Cys Ser Pro Val  
 35 40 45  
 Ala Leu Val Lys Arg Val Gly Ser Leu Met Tyr His Leu Leu Trp Ile  
 50 55 60  
 Ser Asn Asn Val Pro Tyr Phe Phe Ile Ile Ala Ser Gly Arg Trp Glu  
 65 70 75 80  
 Lys Lys Arg Ser Lys Ser Val Tyr Ser Lys Thr Leu Ser Leu Leu Thr  
 85 90 95  
 Phe Gln Lys Asp Phe Met Pro Met Ile Leu Phe Val Phe Leu Val Phe  
 100 105 110  
 Thr Ser Thr Asp Phe Ile Met Ser Glu Thr His Leu Asn Leu Ile Leu  
 115 120 125  
 Val Pro Gly Ile Phe Pro Leu Met His Gln Thr Ser Gly Ser Ile Leu  
 130 135 140  
 Gln Gly Phe Pro Val Ile Cys Gln Thr Thr His Thr Cys Ala Phe Arg  
 145 150 155 160  
 Ser Pro Ile

<210> 233  
 <211> 108  
 <212> PRT  
 <213> Homo sapiens  
 <400> 233

Lys Ala Phe Leu Lys Ile Leu Leu Ala Gly Thr Cys Tyr Arg Glu Asp  
 1 5 10 15  
 Ser Ile His Lys Leu Thr Lys Tyr Phe Pro Ser Tyr Ile Phe Ile Phe  
 20 25 30  
 Ile Asn Ser Phe Leu Asn Asp Ile Tyr Phe Trp Val Phe Thr His Val  
 35 40 45  
 Leu Tyr Met Phe Leu Phe Ser Phe Thr Ile Glu His Thr Leu Tyr Gln  
 50 55 60  
 Pro Glu Ala Ser Glu His Leu Met Gly Ala Lys Asn Lys Lys Lys Thr  
 65 70 75 80  
 Ser Phe Gly Ile Ala Asn Thr Phe His Leu Cys Leu Ile His Ile Lys  
 85 90 95  
 Phe Glu Ser Trp Ala Tyr Tyr Phe Glu His Phe His  
 100 105

<210> 234  
 <211> 145  
 <212> PRT  
 <213> Homo sapiens

<400> 234

Pro Thr Ser Pro Asn Asn Thr Thr Val Phe Ile Ser Phe Phe Arg Ile  
 1 5 10 15  
 Val Phe Phe Leu Tyr Ile Leu Glu Leu Cys Val Cys Gly Pro Ile Gln  
 20 25 30  
 Asn Ala Leu Leu Tyr Asn Cys Thr Phe Thr Gln Gln Met Phe Leu Ile  
 35 40 45  
 Phe Thr His Ala Val Val Cys Ile Arg His Phe Leu Leu Phe Ala  
 50 55 60  
 Met Glu Trp Phe Cys Phe Val Phe Val Leu Phe Lys Asn Ala Glu Phe  
 65 70 75 80  
 Val Tyr Ser Phe Ser Gly Trp Thr Phe Gly Leu Leu Ser Val Leu Gly  
 85 90 95  
 Ser Phe Glu Ser Leu Leu Thr Phe Leu Ser Lys Phe Leu Asn Gly Leu  
 100 105 110  
 Pro Leu Leu Leu Thr Leu Arg Ile Pro Met Ser Gly Ile Thr Asp Leu  
 115 120 125  
 Val Leu Ser Glu Thr Val Arg Pro Phe Phe Ser Pro Ser Gly Cys Ile  
 130 135 140

Ile  
 145

<210> 235  
 <211> 109  
 <212> PRT  
 <213> Homo sapiens

<400> 235

Trp Thr Ala Trp Asp Pro Ser Ile Phe Gly Val Val Gly Asn Leu Val  
 1 5 10 15  
 Ala Ile Val Val Leu Cys Lys Ser Arg Lys Glu Gln Lys Glu Thr Thr  
 20 25 30  
 Phe Tyr Thr Val Met Arg Leu Ala Ala Thr Asp Leu Leu Phe Thr Leu  
 35 40 45  
 Leu Val Ser Gln Val Thr Ile Ala Met Tyr Met Lys Gly Gly Pro Gly  
 50 55 60  
 Gly Gln Leu Leu Cys Glu Tyr Ser Ile Phe Ser Leu Phe Phe Phe Ser  
 65 70 75 80  
 Gln Ser Gly Leu Ser Ile Val Cys Ala Met Ile Ser Ile Gln Val Ile  
 85 90 95  
 Cys Val Arg His Ser Lys Ser Phe Lys Ser Phe Met Phe  
 100 105

<210> 236  
 <211> 181  
 <212> PRT  
 <213> Homo sapiens

<400> 236

Ser Leu Gly Asp Arg Ala Arg Leu Cys Leu Lys Lys Lys Lys Glu Thr  
 1 5 10 15  
 Gly Lys Ser Gln Asp Ser Asn His Val Tyr Val Cys Val Cys Thr Ala  
 20 25 30  
 Trp Val Leu His Leu Leu Tyr Lys Ile Ile Arg Cys Trp Gln Ile Pro  
 35 40 45  
 Arg Pro Val Ala Tyr Val Asn Lys Leu Glu Thr Arg Leu Ser Ala Asn  
 50 55 60  
 Leu Val Ala Leu Cys Arg Gly Pro Trp Glu Gly Asn Cys Leu Gln Ile  
 65 70 75 80  
 Arg Pro Ser Gly His Gly Ser Gln Ser Leu Gly Trp Thr Pro Lys Thr  
 85 90 95  
 His Ser Gly Leu Asn Leu Ala Leu Leu Ser Glu Gln Arg Cys Tyr Lys  
 100 105 110  
 Arg Gln Thr His Thr His Arg Ala Ile Arg Ser Ala Leu Val Asn Met  
 115 120 125  
 Leu Gly Lys Lys Tyr Asp Thr Leu Ala Tyr Leu Ala Ile Phe Phe Lys  
 130 135 140  
 Phe Gln Pro Ser Leu Ile Gly Asp Pro Val Thr His Asp Ser Ser Arg  
 145 150 155 160  
 Lys Arg Leu His Phe Leu Phe Ala Asp Lys Glu Ala Glu Leu Glu Phe  
 165 170 175  
 Ala Val Gly Arg Asp  
 180



<210> 237  
 <211> 208  
 <212> PRT  
 <213> Homo sapiens

<400> 237

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Ser Thr Arg Thr Thr Pro Leu Glu Arg Glu Ser Ala Phe Thr Asp Ile
1          5          10
Asn Leu Ala Pro Gln Lys Phe Leu Val Leu Lys Glu Arg Asp Cys Ile
20        25        30
Trp Thr Leu Ile Pro Lys Glu Lys Glu Pro Glu Thr Asp Asp Ile Lys
35        40        45
Gln Gly Lys Lys Lys Lys Lys Lys Leu Leu Val Ala Gln Lys Gly Val
50        55        60
Asp Gln Ser Leu Asn Tyr Thr Leu Ile Lys Val Asn Tyr Ile Phe Thr
65        70        75        80
Pro Gly Cys Met Trp Trp Ile Leu Ser Ser Phe Leu Leu Val Pro Arg
85        90        95
Cys Ser Leu Ser Gln Trp Lys Leu Leu Gly Glu Lys Gly Gln Glu Val
100       105       110
Leu Ser Phe Leu Ile Trp Pro Leu Ala Pro His Gln His Arg Arg Ala
115       120       125
His His Lys Tyr His Leu Met Ile Phe Phe Pro Arg Ile His Ser Pro
130       135       140
Arg Pro Cys Val Lys Ala Cys Ala Ile Ser Phe Thr Glu Val Leu Leu
145       150       155       160
Ser Leu Gln Val Gly Ser Arg Lys Tyr Gly Ala Arg Lys Thr Leu Lys
165       170       175
Leu Pro Leu Gly Ser Trp Cys Pro Val Met Asp Ala Ile Lys Pro Gln
180       185       190
Thr Gly Trp Cys Ala His Ser His Val Gly Pro Leu Thr Ala Ser Gly
195       200       205

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<210> 238  
 <211> 186  
 <212> PRT  
 <213> Homo sapiens

<400> 238

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Trp Ala Ser Cys Val Leu Ser Val Cys Met Arg Lys Glu Lys Val Tyr
1          5          10
Leu Asn Lys Tyr Tyr Leu Ile Phe Thr Glu Leu Gly Arg Gly Lys Asn
20        25        30
Ala Asn Gln Met Gln Cys Ser Leu Gly Arg Asn Phe Trp Glu Cys Gln
35        40        45
Ser Gly Lys Met Ser Glu Lys Asp Ile Asn Val Pro Leu Lys Lys Ala
50        55        60

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Gln Met Glu Leu Thr Phe Gly Thr Ala Ser Lys Gly Gln Thr Phe Pro  
 65 70 75 80  
 Gln Tyr Cys Pro Ile Ile Lys Tyr Thr Val Asp Arg Gln Gly Pro Pro  
 85 90 95  
 Lys Gln Ser Ile Glu Phe Leu Leu Ile Leu Gly Leu Lys Ile Leu Gly  
 100 105 110  
 Lys Val Asn Leu Lys His Ala Glu Ile Trp Cys Glu Ser Gln Lys Arg  
 115 120 125  
 Lys Lys Asn Pro Glu Ala Ser Cys Leu Ser His Tyr Leu Pro Pro His  
 130 135 140  
 Val Ile Thr Arg Thr Tyr Phe Phe Ser Phe Phe Arg Ser Asn Ala Phe  
 145 150 155 160  
 Asp Ser Ser Leu Phe Ala Phe Ile Leu Val His Phe Ile Cys Leu Arg  
 165 170 175  
 Val Lys Val Phe Thr Ser Leu Arg Thr Ile  
 180 185

<210> 239  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 239

Trp Ile Phe Ser Lys Val Val Cys Thr Glu Arg Val Glu Gln Lys Ser  
 1 5 10 15  
 Lys Thr Cys Asn Asn Ser Glu Ile Phe Gly Phe Val Thr Thr Glu Lys  
 20 25 30  
 His Cys Trp Arg Cys Met Val Cys Lys Cys Glu Asn Val Pro Leu Ile  
 35 40 45  
 Ala Cys Ile Gln His Glu Gly Leu Leu Phe Val Phe Tyr Phe Ser Asn  
 50 55 60  
 Leu Leu Ser Phe Ser Arg Cys Pro Ser His Thr Glu Pro Arg Ser Leu  
 65 70 75 80  
 Thr Gly Val Glu Phe Leu Leu Leu Gly Leu Ser Gly Asp Pro Glu Leu  
 85 90 95  
 Gln Pro Val Leu Ala Leu Leu Ser Leu Ser Leu Ser Met Tyr Leu Val  
 100 105 110  
 Thr Val Leu Arg Asn Leu Leu Ile Ile Leu Ala Val Asn Pro Asp Ser  
 115 120 125  
 His Leu His Thr Pro Met Tyr Phe Phe Leu Ser Asn Leu Cys Trp Ala  
 130 135 140  
 Asn Leu Ser Phe Thr Ser Ala Thr Val Pro Lys Met Thr Val Asp Met  
 145 150 155 160  
 Gln Leu His Ser Arg Val Ile Ser His Ala Gly Cys Leu Thr Gln Met  
 165 170 175  
 Ser Phe Leu Val Leu Phe Ala Cys Ile Glu Asp Met Leu Leu Thr Met

180                                      185                                      190  
 Met Ala Tyr Asp Cys Phe Val Ala Ile Leu Ser Pro Ser Ala Leu Pro  
       195                                      200                                      205  
  
 Ser His Cys Glu Ser  
       210  
  
 <210> 240  
 <211> 200  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 240  
  
 Met Cys Asn Tyr Ser Thr His Gln Leu Tyr His Phe Asn Ser Leu Tyr  
   1                                      5                                      10                                      15  
  
 Ile Val Pro Gln Val Ser Phe Ser Asn Gly His Tyr Gly Leu Ser Thr  
           20                                      25                                      30  
  
 Lys Tyr Pro Phe Ser Pro Phe Pro Leu Ile Leu Glu Thr Asp Leu Phe  
           35                                      40                                      45  
  
 Ser Tyr Leu Thr Phe Pro Ser Leu Ser Leu Cys Leu Gly Gly Ser Ser  
   50                                      55                                      60  
  
 Asn Pro Val Ser Ala Met Cys Phe Ile Val Gln Gly Tyr Phe Ile Cys  
   65                                      70                                      75                                      80  
  
 His Asp Asn Asn Trp Phe Arg Asp Gly Gln Ile Ile Lys Phe Trp Pro  
           85                                      90                                      95  
  
 Ile Arg Cys Lys Arg Asp Ser Lys Lys Glu Thr Phe Ser Ile Leu Pro  
           100                                      105                                      110  
  
 Leu Val Ser Ser Met Val Leu Leu Lys Val Leu Pro Ser Tyr Glu Ser  
           115                                      120                                      125  
  
 Arg Thr Lys Asp Ser Glu Met Ala Arg Lys His Glu Pro Arg Ser Trp  
           130                                      135                                      140  
  
 Ile Thr Leu Leu Ile Tyr Tyr Ile Lys Gln Ser Trp Arg Pro His Tyr  
   145                                      150                                      155                                      160  
  
 His Tyr Asn Cys Arg Tyr Val Ile Thr Lys Val Leu Phe Gly Trp Ile  
           165                                      170                                      175  
  
 Leu Phe Tyr Phe Leu Gln Val Ser Lys Tyr Leu Thr Ile Cys His Pro  
           180                                      185                                      190  
  
 Ile Ala His Leu His Gln Gly Asn  
       195                                      200  
  
 <210> 241  
 <211> 195  
 <212> PRT  
 <213> Homo sapiens  
  
 <400> 241  
  
 Leu Ala Asn Thr Asn Gln Asn Val Ser Asn Tyr Pro Ser Phe Leu His  
   1                                      5                                      10                                      15  
  
 Phe Lys Ile Pro Pro Phe Ile Thr His Gln Ile Leu Thr Ser Thr Glu

20					25					30					
Ser	Leu	Ser	Gln	Phe	Ser	Ile	Leu	Phe	Tyr	Arg	Ser	Val	Gly	Leu	Phe
		35					40					45			
Leu	Gly	Arg	Tyr	Tyr	Lys	Met	Thr	Leu	Phe	Leu	Ile	Arg	Lys	Ala	Ile
	50					55					60				
Lys	Ala	Tyr	Tyr	Arg	Lys	Ile	Arg	Asn	Ile	Thr	Leu	Lys	Asn	Lys	Gln
65					70					75					80
Thr	Lys	Thr	Leu	Val	Leu	Ala	Pro	Arg	Asp	Tyr	Tyr	His	Phe	Thr	Trp
				85					90					95	
Met	Phe	Ile	Thr	Pro	Asp	His	Leu	Ile	Tyr	Ile	Asn	Val	Tyr	Lys	Tyr
			100					105					110		
Val	His	Ser	Ser	Lys	Ile	Glu	Ile	Thr	Pro	Tyr	Lys	Trp	Phe	Cys	Lys
		115					120					125			
Leu	Phe	Ser	Phe	His	Asn	Thr	Ser	Gly	Ile	Cys	Phe	Pro	Cys	Gln	Ile
	130					135					140				
Val	Phe	Phe	Leu	Lys	Leu	Leu	Asn	Cys	Lys	Ile	His	Ala	Tyr	Arg	Lys
145					150					155					160
Val	His	Glu	Ile	Asn	Thr	Phe	Ser	Ser	Met	Ile	Tyr	His	Lys	Ala	Asn
				165					170					175	
Thr	His	Val	Thr	Thr	Thr	Gln	Val	Glu	Lys	Tyr	Asn	Ile	Val	Ser	Ile
			180					185					190		
Pro	Gly	Ser													
		195													

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<210> 242
<211> 225
<212> PRT
<213> Homo sapiens
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<400> 242

Tyr 1	Pro	Ile	Leu 5	Trp	His	Leu	Gly	Arg	Leu 10	Asn	Thr	Leu	Asp	Arg 15	Lys
Leu	Glu	Arg	Pro 20	Gln	Lys	Gln	Ala	Leu 25	Ser	Asp	Leu	Leu	Pro 30	Ser	Ser
Cys	Ser	Ser 35	Val	Ser	Pro	Lys	Ser 40	Lys	Val	Leu	Lys	Thr 45	Arg	Ile	Pro
Leu 50	Pro	Gln	Gly	Arg	Ser	Lys 55	Leu	Glu	Pro	Leu	Tyr 60	Pro	Lys	Ser	Asn
His 65	Lys	Thr	Tyr	Lys	Cys 70	His	Thr	Leu	Pro	Ser 75	Pro	Leu	Arg	Pro	Leu 80
Leu	Asp	Ala	Gly	Pro 85	Pro	Leu	Tyr	Leu	Gly 90	Lys	Arg	His	Pro	Ser 95	Gln
Arg	Asn	Gln	Glu 100	Val	Ser	Glu	Gln	Arg 105	Gly	Leu	Leu	Val	Ser 110	Pro	Leu
Leu	Trp	Phe 115	Gly	Tyr	Gly	Leu	Phe 120	Gly	Pro	Thr	Glu	Ser 125	Tyr	Val	Glu

Ile Phe Gln Cys Cys Lys Trp Gly Val Val Arg Asp Val Trp Ala Met  
 130 135 140  
 Arg Val Asp Pro Ser Val Thr Trp Phe His Ser His Arg Ser Glu Phe  
 145 150 155 160  
 Ser Leu Leu Ala Pro Lys Thr Thr Val Cys Lys Glu Pro Asp Thr Ala  
 165 170 175  
 Ser Ser Leu Pro Leu Ala Ser Cys Pro Gly Val Pro Leu Tyr Thr Ser  
 180 185 190  
 Gly Ser Leu Cys Leu Leu Pro Val Glu Ala Ala Arg Ser Cys Gln Ser  
 195 200 205  
 Arg Cys Cys Tyr Ala Ser Gly Met Ala Ser Arg Thr Val Ser His Ile  
 210 215 220  
 Phe  
 225

<210> 243  
 <211> 219  
 <212> PRT  
 <213> Homo sapiens

<400> 243

Cys Arg Arg Thr Tyr Gly Glu Asn Ser Cys Ile Ala Lys His Glu Ala  
 1 5 10 15  
 His Val Pro Ser Ser Ser Pro Glu Val Cys Leu Phe Met Leu Pro Gly  
 20 25 30  
 Ile Pro Phe Arg Lys Gln Val Asn Gly Ala Phe Cys Thr Phe Met Leu  
 35 40 45  
 Asn Gly Glu Pro Lys Arg Val Thr Thr Pro Leu Gln Cys Leu Leu Gly  
 50 55 60  
 Leu Gly Glu Gln Arg Ser Cys Lys Tyr Glu Val Leu Lys Asp Ser Val  
 65 70 75 80  
 Thr Arg Val Met Ile Phe Gln Tyr Gly Gln Lys Thr Ser Ser Met Gln  
 85 90 95  
 Pro Ser Leu Thr Trp Pro Tyr Lys Thr Lys Val Val Trp Pro Glu Leu  
 100 105 110  
 Glu Gln Leu Gly Trp Met Ala Gln Cys Lys Gly Ala Gly Gly Arg Pro  
 115 120 125  
 Val Asp Pro Thr Leu Gly Trp Pro His Gly Gly Gln Ser Pro Cys Ser  
 130 135 140  
 Leu Lys Trp Pro Thr Pro Val Pro Arg Lys Ala Thr Pro Glu Val Pro  
 145 150 155 160  
 Thr Ile Cys Cys Asn Gln Ile Cys Asn His Arg Leu Phe Leu Ser Arg  
 165 170 175  
 Val Gln Leu Ala Ile Ile Asn Gly Met Asn Gly Ala Pro Gln Met Ser  
 180 185 190

Thr Ala Ser Ser Met Tyr Gly Glu Gln Thr Leu Leu Ser Cys Cys His  
 195 200 205

Val Gly Ile Ser Val Gln Leu Cys Gln Val Phe  
 210 215

<210> 244  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 244

Ile Phe Tyr Leu Arg Asn Phe Phe Gln Leu His Asn Leu Leu Leu Glu  
 1 5 10 15

Met Ser Ser Glu Phe Leu Asp Cys Cys Leu Asn Ser Phe Val Arg Ala  
 20 25 30

Pro Ile Thr Lys Tyr His Arg Leu Gly Asp Leu Tyr Asn Met Asn Leu  
 35 40 45

Phe Ser Gln Ile Leu Glu Ser Gly Cys Ser Ser Arg Cys Arg Gln Val  
 50 55 60

Trp Phe Leu Leu Arg Pro Leu Ser Leu Ala His Arg Arg Thr Ser Ser  
 65 70 75 80

Cys Cys Val Phe Thr Trp Leu Ser Leu Cys Val Cys Leu Cys Pro Asn  
 85 90 95

Leu Leu Phe Leu Gly His Leu Leu Cys Ser Ile Arg Ala His Leu Asn  
 100 105 110

Asp Ser Ile Leu Thr Leu Ala Leu Arg Tyr Phe Leu Gln Ile Gln Thr  
 115 120 125

His Phe Lys Val Leu Arg Arg Arg Phe Asn Phe Met Asn Phe Arg Gly  
 130 135 140

Asp Thr Asn Gln Leu Ile Thr Gln Cys Tyr Val His Asn Lys Phe Asn  
 145 150 155 160

Lys Thr Cys Lys Asn Ile Phe Gln Ile Leu Ser Tyr Asn Phe Pro Cys  
 165 170 175

Ala Val Ile Asp Pro Lys Tyr Ser Glu Leu Leu Thr Phe Leu Ile Trp  
 180 185 190

Leu Gly Pro His Tyr Ile Ser Leu Leu Pro Ser Leu Cys Arg His Gln  
 195 200 205

Ser Ser Lys Lys Gly  
 210

<210> 245  
 <211> 227  
 <212> PRT  
 <213> Homo sapiens

<400> 245

Pro Ser Pro Gln Ser Leu Ser Gln Trp Met Val Leu Lys Asn Thr Cys  
 1 5 10 15

Ile Glu Cys Ile Leu Val Ser Gly Met Pro Leu Thr Pro Glu Gly Glu  
 20 25 30  
 Val Leu Glu Gly Arg Asn Cys Ser Trp Ala Leu Gly Gln Gly Asp Leu  
 35 40 45  
 Asp Ser Ser Pro Ala Ser Leu Thr Tyr Trp Leu Trp Ala Asn Tyr Leu  
 50 55 60  
 Thr Trp Leu Ser Leu Gly Phe Leu Ile Cys Glu Met Gln Leu Leu Gly  
 65 70 75 80  
 Phe Asp Glu Pro Met His Met Arg Leu Glu Glu Tyr Trp Leu Met Gln  
 85 90 95  
 Gly Leu Pro Leu Val Leu Ser Leu His Pro Trp Ser Leu Ala Leu Cys  
 100 105 110  
 Arg Ala Gly Arg Met Gln Val Leu Gly Arg Trp Ala Trp Leu Met Gly  
 115 120 125  
 Val Ala Val Ala Phe Ala Asp Glu Tyr Glu Cys Gln Ala Cys Pro Asn  
 130 135 140  
 Asn Glu Trp Ser Tyr Gln Ser Glu Thr Ser Cys Phe Lys Arg Gln Leu  
 145 150 155 160  
 Val Phe Leu Glu Trp His Glu Ala Pro Thr Ile Ala Val Ala Leu Leu  
 165 170 175  
 Ala Ala Leu Gly Phe Leu Ser Thr Leu Ala Ile Leu Val Ile Phe Trp  
 180 185 190  
 Arg His Phe Gln Thr Pro Ile Val Arg Ser Ala Gly Gly Pro Met Cys  
 195 200 205  
 Phe Leu Met Leu Thr Leu Leu Leu Val Ala Tyr Met Val Val Pro Val  
 210 215 220

Tyr Val Gly  
225

<210> 246  
 <211> 221  
 <212> PRT  
 <213> Homo sapiens

<400> 246

Val Glu Ser Asn Asp Val Leu Leu Ser His Arg Val Lys Lys Leu Asp  
 1 5 10 15  
 Ile Gly Ser Asn Gln Asn Pro His Cys Ile Pro Ser Pro Lys Val Thr  
 20 25 30  
 Thr Phe Leu Thr Ser Ile Asp Leu Phe Ile Asn Ser Phe Thr Asp Thr  
 35 40 45  
 Ile Ile Ser Tyr Lys Tyr Gln Asn Leu Asp Thr Pro Phe Arg Asn Asn  
 50 55 60  
 Phe Asn Gln Val Phe Ser Phe Arg Met Phe Asn Tyr Thr Leu Arg Tyr  
 65 70 75 80  
 Ile Tyr Leu Asn Val Cys Leu Phe Lys Tyr Val Asp Tyr Val Leu Leu

85 90 95  
 Pro Lys Lys Val Leu Lys Leu Leu Pro Ser Leu Ala Ala His Lys Ile  
 100 105 110  
 Lys Lys Ser Arg Gln Met Tyr Pro Trp Leu Ala Phe Ser Tyr Gln Gln  
 115 120 125  
 Lys Asp Trp Phe Tyr Ser Asn Asn Ile Lys Asn Ala Gly Phe Asn His  
 130 135 140  
 Ile Cys Ile Tyr Thr His Thr His Ile Tyr Asp Phe Thr Tyr Ile Ser  
 145 150 155 160  
 Tyr Lys Tyr Asp Phe Lys Pro Leu His Leu Tyr Ile Phe Leu Tyr Lys  
 165 170 175  
 Tyr Tyr Ile Tyr Phe Ile Phe Tyr Ile Tyr Phe Ile Tyr Phe Tyr Ile  
 180 185 190  
 Leu His Thr Phe Tyr Val Tyr Leu Ile Phe Tyr Ile Tyr Leu Tyr Tyr  
 195 200 205  
 Ile Tyr Phe Ile Leu Pro Phe Leu Tyr Ile Tyr Thr His  
 210 215 220

<210> 247  
 <211> 157  
 <212> PRT  
 <213> Homo sapiens

<400> 247

Val Gln Arg Arg Asp Ile Phe Thr His Ile Asn Thr Ile Phe Arg Phe  
 1 5 10 15  
 Tyr Leu Ser Tyr Asn Ser Asn Pro Cys His Ser Asp Ser Asn Ile Leu  
 20 25 30  
 Ala Phe Glu Ser Ser Ile Met Leu Ala Phe Leu Leu Lys Thr Cys Ser  
 35 40 45  
 Ala Phe Lys Thr Gln Ile Ser Tyr Tyr Leu Val Leu Lys His Phe Pro  
 50 55 60  
 Thr Leu Leu Val Met Thr Thr Tyr Phe Cys Val Lys Leu Cys Met Tyr  
 65 70 75 80  
 Cys Phe Thr Phe Asp Ile Leu Leu Ser Leu Phe Val Cys Met Thr Ala  
 85 90 95  
 Phe Phe Phe Leu Leu Asp His Lys Leu Leu Glu Tyr Lys Asn Leu Leu  
 100 105 110  
 Ile Phe Ile Ser Ser Val Phe Thr Thr Val Phe Gly Lys Tyr Ser Val  
 115 120 125  
 Asn Met Asn Ile Lys Glu Thr Tyr Leu Lys Tyr Val Ile Ile Phe Tyr  
 130 135 140  
 Glu Cys Phe Leu Gln Gly Ser Asp Asn Glu Glu Gly Val  
 145 150 155

<210> 248  
 <211> 220



<212> PRT  
 <213> Homo sapiens

<400> 248

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Gly His Ile His Leu Arg Cys Val Val Lys Pro Glu Thr Pro His
1           5           10           15
Thr Tyr Val His Pro Leu Gly Phe Leu Phe Pro Gly Asp Leu Leu His
20           25           30
Phe Cys Pro Lys Met Leu Ala Asn Leu Ile Ser His Ile Lys Ser Ile
35           40           45
Ser Tyr Ala Gly Cys Leu Leu Gln Phe Phe Tyr Phe Ser Met Cys Ala
50           55           60
Ala Glu Gly Tyr Phe Leu Ser Val Met Ser Phe Asp Arg Phe Leu Thr
65           70           75           80
Ile Cys Arg Pro Leu His Tyr Pro Thr Val Met Thr His His Leu Cys
85           90           95
Val Arg Leu Val Ala Phe Cys Arg Ala Gly Gly Phe Leu Ser Ile Leu
100          105          110
Met Pro Ala Val Leu Met Ser Arg Val Pro Phe Cys Gly Pro Asn Ile
115          120          125
Thr Asp His Phe Phe Cys Asn Leu Gly Pro Leu Leu Ala Leu Ser Cys
130          135          140
Ala Pro Val Pro Lys Thr Thr Leu Thr Cys Ala Thr Val Ser Ser Leu
145          150          155          160
Ile Ile Phe Ile Thr Phe Leu Tyr Ile Leu Gly Ser His Ile Leu Val
165          170          175
Leu Arg Ala Val Leu Trp Val Pro Ala Gly Ser Gly Arg Asn Lys Ala
180          185          190
Phe Ser Thr Cys Ala Ser His Phe Leu Val Val Ser Phe Phe Tyr Gly
195          200          205
Ser Val Met Val Met Tyr Val Ser Pro Gly Ser Arg
210          215          220

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<210> 249  
 <211> 180  
 <212> PRT  
 <213> Homo sapiens

<400> 249

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Ala Ala Ser Cys Thr Ser His Pro Ala Phe Pro Phe Arg Pro Pro Asn
1           5           10           15
Asn Ala Ala Lys Gly Asn Trp Asn Pro Gln Pro Glu Leu Pro Ser Leu
20           25           30
Lys Pro Thr Val Pro His Val Ala His His Thr Ala His Gln Arg Ser
35           40           45
Thr Asn Leu Val Ser Asp Val Val Pro Glu Ile Ile Arg Tyr Ser Gln
50           55           60

```

Pro Glu Pro Val Ser Leu Ala Ser Pro Leu Ile Leu Asn Arg Ile Arg  
 65 70 75 80  
 Ser Ser Ala Ala Phe Leu Lys Ala Ala Gly Arg Gln Ser Ser Cys Leu  
 85 90 95  
 Thr Leu Phe Ala Trp Trp His Gln Pro Ser Ile Thr Asn Thr Phe Leu  
 100 105 110  
 Ser Ser Arg Trp Pro Asp Ser Ile Pro Trp His Ser Pro Gln Gln Ser  
 115 120 125  
 Leu Lys Ser Gly Asn Trp Asp His Arg Glu Phe Gln Lys Glu Ile Leu  
 130 135 140  
 Ala Asp Ser Lys Thr Arg Asp Arg Pro Ala Ile Leu Glu Arg Ile Pro  
 145 150 155 160  
 Val Pro Pro Pro Phe Thr Asp Asn Ser Thr Val Gln Glu Val Met His  
 165 170 175  
 Ala Gln Gly His  
 180

<210> 250  
 <211> 93  
 <212> PRT  
 <213> Homo sapiens

<400> 250

Leu Lys Tyr Ser Asn His Asp Ile Cys Glu Phe Ser Met Lys Lys Arg  
 1 5 10 15  
 Gly Lys Leu Ala Arg Tyr Ser Asp Asp Lys Ser Leu Phe Leu Leu Tyr  
 20 25 30  
 Phe Ser Ile Cys Thr Ile Thr Pro Gly Glu Ile Met Glu Met Arg Asn  
 35 40 45  
 Thr Thr Pro Asp Phe Ile Leu Leu Gly Leu Phe Asn His Thr Arg Ala  
 50 55 60  
 His Gln Val Leu Phe Met Met Val Leu Ser Ile Val Leu Thr Ser Leu  
 65 70 75 80  
 Phe Gly Asn Ser Leu Met Ile Leu Leu Ile His Arg Asp  
 85 90

<210> 251  
 <211> 105  
 <212> PRT  
 <213> Homo sapiens

<400> 251

Arg Leu His Thr Pro Met Tyr Phe Leu Leu Ser Gln Leu Ser Leu Met  
 1 5 10 15  
 Asp Val Met Leu Val Ser Thr Thr Val Pro Lys Met Ala Ala Asp Tyr  
 20 25 30  
 Leu Thr Gly Asn Lys Ala Ile Ser Arg Ala Gly Cys Gly Val Gln Ile  
 35 40 45

Phe Phe Leu Leu Thr Leu Gly Gly Gly Glu Cys Phe Leu Leu Ala Ala  
 50 55 60  
 Met Ala Tyr Asp Arg Tyr Ala Ala Val Cys His Pro Leu Arg Tyr Pro  
 65 70 75 80  
 Thr Leu Met Ser Trp Gln Leu Cys Leu Arg Met Thr Met Ser Ser Trp  
 85 90 95  
 Leu Leu Gly Ala Ala Asp Gly Leu Leu  
 100 105

<210> 252  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 252

Met Ser Leu Gly Phe Ser Glu Ile Glu His Phe Gly Gln Ala Val Gly  
 1 5 10 15  
 Ser Leu Tyr Asp Cys Leu Asp Thr Ala Lys Gly Thr Phe Phe Leu Ser  
 20 25 30  
 Pro Asp Ser Glu Val Leu Glu Thr Ala Val Ala Leu Ala Thr Gly Cys  
 35 40 45  
 Val Asp His Leu Arg Met Thr Trp Gly Ser Val Leu Cys Thr Leu Glu  
 50 55 60  
 Pro Ile Gly Ser Leu Gln Trp Val Pro Trp Cys Thr Gln His Gln Ala  
 65 70 75 80  
 Val Arg Thr Thr Pro Asn Gly Leu Gly Gly Arg Ser Lys Thr Thr Gly  
 85 90 95  
 Ser Val Pro Val Leu Thr Pro Leu Cys Pro His Arg Pro Gly Leu Gln  
 100 105 110  
 Gly Pro Cys Pro Ser Arg Ala Glu Asn Val Val Leu Trp Glu Pro Ser  
 115 120 125  
 Gly Pro Leu Gly Pro Gln His Trp Ala Met Gly Ser Ser Leu Pro Glu  
 130 135 140  
 Thr Gly Ala Trp Gly Cys Ser Ile Gln Leu Pro Lys Pro Lys Arg His  
 145 150 155 160  
 Trp Asp Arg Trp Pro Ser Arg Leu Arg Asp Ala Gln Val Pro Glu Val  
 165 170 175  
 Gly Arg Ala Leu Gly Gly Val Pro Thr Ala Ile Leu Gln Ile Gln Lys  
 180 185 190  
 Leu Arg Pro Arg Glu Gly Glu Arg Phe Ala Glu His Ala Gln Gln Ala  
 195 200 205  
 Ser Gly Arg Ala Gly  
 210

<210> 253  
 <211> 206  
 <212> PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 253

Arg Trp Ala Glu Ser Ile Phe Ile Thr Lys Val Ser Gly Ala Gln Ala  
 1 5 10 15  
 Lys Pro Ala Ala Phe Gln Gly Lys His Ser Val Leu Val Leu Leu Leu  
 20 25 30  
 Asp Cys Leu Ser Glu Val Thr Asp Trp Ile Lys Gln Asn Thr Pro Glu  
 35 40 45  
 Ile Phe Thr Lys Lys Val Arg Ser Lys Arg Lys Val Val Lys Gly Asn  
 50 55 60  
 Val Leu Ser Asn Gly Trp Leu Met Ser Lys Ser Ser Leu Lys Ile Tyr  
 65 70 75 80  
 Leu Phe Ser Ser Phe Arg Lys Ala Thr Glu Met Gln Thr Gly Ala Ile  
 85 90 95  
 Asn Asn Ile Val Leu Glu Asp Asn Leu Lys Ile Val Pro Lys Met Pro  
 100 105 110  
 Phe Val Thr Val Ile Leu His Leu Asn His Trp Gln Phe Gly Met Thr  
 115 120 125  
 Val Phe Cys Thr Ala Arg Cys Thr Leu Tyr Tyr Ile Arg Glu Arg His  
 130 135 140  
 Ala Cys Ala Pro Pro Ser Ser Pro His Lys Ser Pro Gly Gly His Lys  
 145 150 155 160  
 Asn Val Val Pro Pro Gly Val Ser Lys Asn Leu Thr Arg Lys Tyr Ile  
 165 170 175  
 Leu Ile Leu His Leu Gly Asn Val Val Ile Ser Leu Met Leu Ile Phe  
 180 185 190  
 Ile Ser Pro Ser Ser Ser Cys Leu Tyr Glu Leu Leu Leu Ser  
 195 200 205

&lt;210&gt; 254

&lt;211&gt; 214

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 254

Tyr Ala Met Leu His Thr His Cys Trp Trp Leu Pro Ser Ile Ser Tyr  
 1 5 10 15  
 Ser Val Thr Ile Asn Ser His Phe Ser Leu Ser Pro Tyr Thr Phe Pro  
 20 25 30  
 Ser Leu Ser Asp Ala Thr Val Pro Ser Phe Arg Thr Leu Leu Thr Phe  
 35 40 45  
 Phe Ser Ala Phe Leu Leu Lys Ile Asn Phe Tyr Leu Leu Thr Leu Tyr  
 50 55 60  
 Thr Phe Met Gly Tyr Ser Val Met Phe Gln Val Tyr Thr Leu His Asp  
 65 70 75 80

Asp Gln Ile Met Val Ile Thr Val Phe Thr Thr Leu Asn Ile Asp His  
                     85                    90                    95  
 Phe Leu Val Val Ile Thr Phe Lys Ile Phe Ser Ser Ser Tyr Leu Lys  
                     100                    105                    110  
 Ser Ile His Tyr Ile Val Val Cys Gln Arg His Pro Thr Val Gln Gln  
                     115                    120                    125  
 Asn Thr Arg Thr Tyr Ser Ser Leu Leu Cys Thr His Trp Pro Thr Ser  
                     130                    135                    140  
 Pro Asp Pro Ser Ser Pro Leu Pro Ser Pro Thr Val His Phe Leu Asn  
                     145                    150                    155                    160  
 Glu Thr Cys Ile Ser Leu Thr Tyr Leu Ile Tyr Asn Tyr Val Cys Asn  
                     165                    170                    175  
 Ser Ile Lys His Ile Ser Asn Trp Pro Asp Thr Cys Leu Leu Ile Ser  
                     180                    185                    190  
 Ser Tyr Leu Leu His Tyr Thr Gly Asn Ser Lys Gln Lys Asn Asn Arg  
                     195                    200                    205  
 Leu Asn Phe Tyr Leu Val  
                     210

<210> 255  
 <211> 208  
 <212> PRT  
 <213> Homo sapiens

<400> 255

Ala Ala Cys Ile Ile Ser Leu Val Thr Leu Asp Arg Glu Thr Arg Leu  
 1                    5                    10                    15  
 Cys Ser Gly Ser Trp Ala Ser Ala Cys Ala Gly Asn Ala Val Ser Ile  
                     20                    25                    30  
 Tyr Ile Leu Asn Leu Ala Ala Ala Asp Phe Leu Phe Leu Ser Gly His  
                     35                    40                    45  
 Val Ile Arg Ser Ala Ser Leu Leu Ile Asn Ile Cys His Pro Ile Ser  
                     50                    55                    60  
 Lys Ile Leu Ile Pro Val Met Thr Phe Leu Tyr Phe Thr Gly Leu Ser  
                     65                    70                    75                    80  
 Phe Leu Ser Ala Met Ser Thr Glu Arg Cys Leu Cys Val Leu Trp Pro  
                     85                    90                    95  
 Ile Trp Tyr Arg Cys Leu Leu Pro Pro His Thr Cys Gln Arg Ser Cys  
                     100                    105                    110  
 Val Ser Cys Phe Gly Pro Cys Pro Tyr Cys Gly Ala Ser Trp Ser Glu  
                     115                    120                    125  
 Cys Ser Val Thr Ser Cys Leu Val Met Leu Ile Leu Phe Gly Val Asn  
                     130                    135                    140  
 His Gln Ile Ser Ser Gln Ser Cys Gly Phe Phe Tyr Val Trp Phe Ser  
                     145                    150                    155                    160  
 Val Gly Pro Ala Trp Ser Cys Leu Gly Phe Ser Val Asp Pro Gly Arg

165 170 175  
 Cys Leu Pro Gly Cys Thr Arg Ser Cys Ser Gln Cys Ser Ser Tyr Ser  
 180 185 190  
 Ala Ala Cys Pro Ser Ala Phe Gly Gly Leu Cys Leu Leu Gly Tyr Thr  
 195 200 205  
 <210> 256  
 <211> 178  
 <212> PRT  
 <213> Homo sapiens  
 <400> 256  
 Pro Leu Ser Pro Leu Ser Lys Trp His Asp His Ala Leu Ser Val Ser  
 1 5 10 15  
 Gly Lys Lys Ser Ala Asp His Lys Gly Ile His Cys Ser Pro Cys Pro  
 20 25 30  
 Ser Leu Ser Pro Val Lys Pro Ser Leu Leu Gln Lys Leu Leu Thr Leu  
 35 40 45  
 Cys Ile Tyr Ile Cys Leu Pro Glu Phe Ile Leu Ser Met Arg Gln Ser  
 50 55 60  
 Arg Leu Met Cys Ser Leu Thr Leu Pro His Gln His Phe Leu Ile Thr  
 65 70 75 80  
 Ser Ile Ile Arg Leu Gly Phe Leu Pro Met Gly Tyr Arg Ile Ser Ile  
 85 90 95  
 Ile Ser Leu Leu Pro Thr Pro Gly Ala Arg Leu Leu Phe Leu Ser Lys  
 100 105 110  
 Phe Thr Leu Ser Lys Trp Pro Ser Tyr Phe Phe Ser Asn Leu Leu Ile  
 115 120 125  
 Phe Phe Leu Leu Gly Leu Glu Thr Phe Pro Ser Pro Ala Leu Gly Gln  
 130 135 140  
 Met Leu Ile Thr Leu Leu Pro Ala Leu Cys Phe Arg Arg Pro Ser Gln  
 145 150 155 160  
 Ile Lys Thr Glu Asn Val Ser Phe Leu Leu Arg Asn Asn Arg Ser Cys  
 165 170 175  
 Phe Val

<210> 257  
 <211> 191  
 <212> PRT  
 <213> Homo sapiens  
 <400> 257

Leu Trp Ala Leu Ile Asn Phe Phe Ser Asp Phe Phe Ala Gly Asn Thr  
 1 5 10 15  
 Phe Glu Ile Ile Gly Leu Lys Ile Met Arg Lys Lys His Leu Ser Leu  
 20 25 30  
 Val Phe Leu Lys Tyr Val Asn Gln Thr Pro Met Pro Ala Leu Leu Leu

35	40	45
Ser Gln Thr Ser Asp Met Arg His Arg Phe Leu Gln Asn Ser Leu Thr		
50	55	60
Lys Ser His Lys Met Cys Arg Phe Pro Gln Ile Pro Lys Thr Met Glu		
65	70	75
Lys His Ser Asp His Lys Ser Phe Met Gly Ile Ala Glu Arg Arg Gly		
	85	90
Glu Leu Trp Leu Ser Leu Met Pro Trp Asn Val Ser Gly Thr Glu Lys		
	100	105
Pro Lys Ile Glu His Asn Lys His Arg Val Gly Asn Phe His Leu Trp		
	115	120
Gln Gln Lys Lys Ile Asn Phe Pro Glu Pro Ile Ser Leu Lys Gln Asn		
	130	135
Phe Gln His His Ile Phe Lys Val Phe Leu Leu Gly Leu Cys Thr Ser		
145	150	155
His Leu Cys Tyr Leu Phe Ile Leu Pro Tyr Trp Ala Val Ala Tyr Tyr		
	165	170
Cys Leu Ser Phe Tyr Ile Pro Lys Asn Ile Ser Phe Thr Val Gly		
	180	185

<210> 258  
 <211> 9  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <221> misc\_feature  
 <223> Peptide substrate

<400> 258

Ala Pro Arg Thr Pro Gly Gly Arg Arg  
 1 5

The first part of the document discusses the importance of maintaining accurate records of all transactions. It emphasizes that proper record-keeping is essential for the transparency and accountability of the organization. The document then outlines the specific procedures for recording transactions, including the use of standardized forms and the requirement for double-checking entries.

The second part of the document addresses the issue of data security. It highlights the need to protect sensitive information from unauthorized access and disclosure. To this end, the document recommends the implementation of robust security measures, such as encryption and access controls, to safeguard the organization's data.

The third part of the document focuses on the importance of regular audits. It states that audits are a critical component of the organization's internal control system, as they help to identify and correct errors and prevent fraud. The document provides guidance on how to conduct audits effectively, including the selection of audit personnel and the use of audit checklists.

The final part of the document discusses the importance of training and education. It notes that all employees must be properly trained in the organization's policies and procedures to ensure compliance. The document recommends that training programs be developed and implemented regularly to keep employees up-to-date on the latest requirements.